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ARTERIAL CARBON DIOXIDE PRESSURE IN CARDIAC DYSPNOEA[1]

By F. R. FRASER, C. F. HARRIS, R. HILTON, and G. C. LINDER

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The relation of the respiratory movements and of pulmonary ventilation to the respiratory centre has been fully discussed by J. S. Haldane (1), and need not be reconsidered here. It is obvious from the work of Haldane and of the numerous investigators quoted by him that the blood supplied to the respiratory centre is of importance in considering the cause of cardiac dyspnoea, since deficient oxygen supply to the centre, increased carbon dioxide pressure, and increased hydrogen-ion concentration at the centre are each capable of producing increased pulmonary ventilation or hyperpnoea. Peabody and Sturgis (2), and Campbell, Hunt, and Poulton (3), have shown that in cardiac dyspnoea there is an increase in the pulmonary ventilation. A number of workers have studied the oxygen saturation of the arterial blood in cardiac dyspnoea, and there is a general agreement that although there is a degree of unsaturation in some cases, the presence of dyspnoea is frequently associated with normal oxygen saturation. Peters and Barr (4), Cobet (5), and Campbell, Hunt, and Poulton (3) have studied the carbon dioxide pressure of the arterial blood, and their conclusions show a lack of agreement which may be to some extent accounted for by the methods employed and the types of cases studied.

Peters and Barr constructed a carbon dioxide dissociation curve with venous blood, and considered the arterial carbon dioxide pressure to be the pressure corresponding to the point on this curve where it was intersected by the ordinate representing the actual carbon dioxide volume in the arterial blood obtained by radial puncture. They obtained values in three cases of mitral stenosis and in one of aortic regurgitation, and considered that these values were within the normal limits, but high relatively to the height of the dissociation curves. In two of their cases second values were obtained when the patients were somewhat recovered from their dyspnoea, and it is of interest that the values in the stage of partial recovery were in each case higher than when the dyspnoea was more pronounced. They found that the arterial carbon dioxide pressure was consistently higher than the alveolar pressure, and concluded that there was a carbon dioxide retention in cardiac dyspnoea.

Campbell, Hunt, and Poulton used the same method as that employed by Peters and Barr, and studied eight cases of mitral stenosis and eight cases of

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cardio-renal disease with pulmonary complications. They found that in mitral stenosis the arterial carbon dioxide pressure is sometimes lower and sometimes higher than normal, and they considered the venosity of the blood due to stasis in the systemic capillaries to be probably the most important factor in cardiac dyspnoea. The high carbon dioxide pressures in some cases of mitral stenosis, and the constantly high values in the elderly patients with cardio-renal disease, they considered to be the result of secondary lung changes and to be contributory factors in causing the dyspnoea.

Cobet obtained a figure for the carbon dioxide pressure of the arterial blood by constructing a dissociation curve with venous blood and by assuming the carbon dioxide content of capillary blood to be the same as that of the arterial blood. The capillary blood was obtained under oil from an incision in the finger after the arm had been immersed in a hot bath, and Lundsgaard and Möller (6) showed that blood obtained in this way is identical with arterial blood. Cobet divided his cases with dyspnoea into three groups, according to the absence or presence of lung complications and the retention of acid bodies other than carbon dioxide. He found normal values in compensated heart disease, low values in cases of mitral valve disease and heart failure, high values in the presence of lung complications, and low values in the cases with retention of acids other than carbon dioxide.

The accuracy of the methods employed by Peters and Barr, Cobet, and Campbell, Hunt, and Poulton depends on the justification of their assumption that the conclusions derived from the carbon dioxide dissociation curve constructed with venous blood represent the conditions in the arterial blood. Morawitz and Walker (7), and Meakins, Dautrebande, and Fetter (8), have shown that venous blood in the presence of stasis has not the same carbon dioxide capacity as arterial blood. Stasis is likely to be present in cases of heart failure with dyspnoea, and Fraser, Graham, and Hilton (9) showed that the dissociation curves constructed with venous and with arterial blood in cases of heart failure are not identical. In the investigations to be reported here, the arterial carbon dioxide pressure has been determined by means of dissociation curves constructed with arterial blood, and a second method has been employed in addition as a check. The oxygen saturations of the arterial blood and the hydrogen-ion concentrations have also been determined, and the significance of the findings in relation to the mechanism of cardiac dyspnoea will be discussed.

Methods.

Fifty cubic centimetres of arterial blood were withdrawn from the femoral artery, without exposure to air, into a syringe well coated with liquid paraffin. The syringe contained powdered potassium oxalate and sodium fluoride in sufficient quantity to give a concentration of 0·4 per cent. of the former and 0·1 per cent. of the latter when dissolved in the blood. The blood was transferred under paraffin to a large test-tube surrounded by ice, and portions were

removed when necessary for the subsequent examinations. Four portions of 10 c.c. were successively transferred to tonometers of 400 c.c. capacity which had previously been filled with mixtures of air and carbon dioxide, such that they contained carbon dioxide at partial pressures of approximately 20 mm., 30 mm., 40 mm., and 50 mm. of Hg. Each tonometer was then placed in a water bath at 37° C. and rotated continuously for fifteen minutes. At the end of that period the pressure in the tonometer was measured while it was still in the bath by connecting the tonometer with a mercury manometer by means of lead tubing of narrow bore. The blood was then run off into a small tube under paraffin, and was chilled again with ice. The carbon dioxide content of the arterial blood and of the samples from the tonometers was estimated by the method of van Slyke and Neill (10) (constant-volume apparatus). The carbon dioxide in the tonometers was meanwhile analysed by the Haldane gas analysis apparatus, and its partial pressure determined. At the same time the pH of the arterial blood and of the blood from the tonometers was being determined by the colorimetric method of Hastings and Sendroy (11). In three of the earlier cases (Nos. 7, 11, and 12) the Dale-Evans (12) method was used, but this was found to be less satisfactory than that of Hastings and Sendroy and was discarded. The oxygen content of the arterial blood and the oxygen capacity were determined by the Haldane apparatus for blood gas analysis.

The volumes of carbon dioxide in the blood from the tonometers were plotted against the pressures of carbon dioxide in the tonometers, and a dissociation curve constructed. The point on the curve corresponding to the carbon dioxide volume of the arterial blood gave an estimation of the arterial carbon dioxide pressure. For the reasons given above, this curve constructed with arterial blood has been considered as representing the conditions of the arterial blood in the body more truly than a curve constructed with venous blood. The loss of carbon dioxide capacity that occurs in shed blood on standing, owing to glycolysis, is hindered to a large extent by the addition of the sodium fluoride, but little is known of the changes that may occur in blood from diseased persons when treated in a tonometer in this way, and it is possible that such a curve does not represent the true arterial conditions in diseased states. A second method of estimating the pressure has therefore been employed. The carbon dioxide pressures of the tonometers were plotted against the pH of the blood from the tonometers as determined by the colorimetric method. The point on the curve constructed in this way that corresponded to the pH of the arterial blood gave a second estimation of the arterial carbon dioxide pressure. If the blood in the tonometers had lost carbon dioxide capacity through glycolysis or other similar change, the dissociation curve would be lower than it should be, and the estimation of the arterial carbon dioxide pressure would be too high, but, on the other hand, the pH curve would be shifted in such a direction that the estimation of the arterial carbon dioxide pressure from it would be too low. A close agreement between the two estimations would thus indicate that this possible error had been avoided or was minimal. The carbon dioxide volume of blood can be

determined with much greater accuracy than the pH by the methods employed, and the value for the carbon dioxide pressure as estimated by means of the dissociation curve has been regarded as the more accurate, but whenever the values as estimated by the two methods differed greatly, the results of the experiment have been discarded. The chart shows the curves obtained in this way in a normal subject, and the values for the arterial carbon dioxide pressure.

Another possible source of error is due to the change in carbon dioxide capacity that results from altering the oxygen saturation of blood. The blood from the tonometers was fully saturated with oxygen, while the arterial blood was not. In the case of arterial blood in healthy persons, which is about 95 per cent. saturated, the error due to this factor is negligible. In only three of the observations here reported was the oxygen saturation of the arterial blood below 90 per cent., and although there may be a small error, especially in these instances, it has not been considered sufficient to need correction in view of the possible experimental errors that are inherent in the methods of analysis and in the manipulations.

Values for the pH of plasma as determined by the colorimetric method agree closely with those obtained electrometrically in normal subjects, but there is not sufficient evidence that the colorimetric method gives values in the case of the blood of diseased persons that are in agreement with electrometric standards. The variations in the haemoglobin, protein, and salt contents of blood in disease may therefore result in values that are not satisfactory for comparison with electrometric standards. The errors due to these factors will, however, be constant in the blood used in the construction of any one pH-carbon dioxide pressure curve, and will not invalidate the figures obtained for the arterial carbon dioxide pressure by means of this curve. The pH of the arterial blood as determined by the colorimetric method will, however, not be satisfactory for comparison with normal standards. Hastings and Sendroy believed that by their method of reading the colorimetric pH at 38° C., the colorimetric reading was the same as the true pH determined electrometrically or from the Hasselbalch formula, all errors due to the dye, salts, and protein being eliminated. Austin, Stadie, and Robinson (13) reopened the question, having found considerable differences between the colorimetric readings at 38° C. and the true pH. They recommended that a correction should be obtained by analysis of true plasma from blood equilibrated at a carbon dioxide pressure close to that expected in the arterial blood, by calculation of its true pH by the Hasselbalch formula, and by comparison of this with the observed colorimetric pH. Their paper appeared when most of the work reported here had been completed, so that the necessary data for applying their corrections were not available. Cullen, Keeler, and Robinson (14) examined fifteen pathological sera from various types of cases and found from electrometric data that pK was very constant at a value of 6·10. By taking this figure of 6·10 as the pK of serum and the values $pK_{blood}-pK_{serum}$ from the nomogram of van Slyke, Hastings, Murray, and Sendroy (15) the pK of the samples of blood was obtained, and values for their true pH

have been calculated from the Hasselbalch equation, using for the carbon dioxide pressures the values obtained from the dissociation curves. These calculated values only are recorded in Table III, but in Table I the values obtained by the Hastings-Sendroy method, without corrections, are given for comparison with them. It will be seen that the values obtained by the two methods may differ considerably, which is in agreement with the experience of Austin, Stadie, and Robinson.

To indicate the quantity of alkali available for combination with the carbon dioxide or the height of the dissociation curve, the carbon dioxide volume corresponding on the curve to a pressure of 40 mm. of Hg has been added to the other determinations recorded in the tables.

Material.

Seventeen cases with heart failure and dyspnoea have been studied. Seven patients with mitral stenosis were selected, since this form of heart disease occurs in younger patients in whom pulmonary, arterial, and renal diseases are unlikely to be present, and because marked dyspnoea occurs in cases of mitral stenosis before the advanced stage of failure is reached, with the consequent severe congestion of the lungs and kidneys. The remaining cases consisted of six with myocardial degeneration, high blood pressure, and arterial disease, two with definite pulmonary disease in addition to heart failure, and two that could not be placed in any of the above groups. Thirty observations were made on these seventeen cases. The results are recorded in Table III, and Case Reports are appended.

Results.

It is difficult to decide on the variations of arterial carbon dioxide pressure in health. The carbon dioxide pressure in the alveolar air is probably almost identical with that in the arterial blood in healthy individuals, and Peters, Barr and Rule (16) collected the published figures and found them to vary from 35·0 to 40·8 mm. of Hg. Figures based on the carbon dioxide dissociation curve and the arterial carbon dioxide volume have been published and show an even greater variation than this, but in these observations the dissociation curves were constructed with venous blood.

The amount of alkali available for combination with carbon dioxide, or the carbon dioxide capacity as indicated by the volume of carbon dioxide in the blood after exposure to a pressure of 40 mm. of Hg, also varies greatly in health. Peters, Barr, and Rule, from their own observations and those of others, concluded that variations from 43·3 to 55·9 volumes per cent. occur in healthy subjects, though it is more constant in any one individual. It is possible that the use of arterial blood instead of venous would show that these limits are too wide. Table II shows that in one healthy subject observed on three occasions over a period of eight months the figures varied from 48·5 to 53·2 volumes per cent.

Austin (17) gives the normal variation in the pH of the arterial blood as 7·30–7·50, and Campbell, Hunt, and Poulton (3) found a variation of 7·35–7·48 in nine patients without breathlessness.

It is obvious, in view of the wide variations that can occur in the carbon dioxide pressure, the available alkali, and the pH of the arterial blood in health, that much caution must be used in concluding that figures for these factors indicate significant departures from the normal. Changes from one observation to another in the same individual under resting conditions in bed in hospital will, however, be of greater significance.

With these qualifications the normal variations have been regarded as (1) carbon dioxide pressure, 35·0–41·0 mm. of Hg; (2) carbon dioxide capacity (at 40 mm. of Hg), 43–56 volumes per cent.; and (3) pH 7·30–7·50.

The arterial carbon dioxide pressures are below the normal values in Cases 1, 2 (first admission), 3, 8, 9, 10, 11, 13, and 14 (first admission), within the normal limits in Cases 2 (second admission), 4, 7, 12 (third observation), 16 and 17, and raised above the normal in Cases 5, 6, 12, 14 (second admission), and 15.

The cases showing low arterial carbon dioxide pressures include three (Cases 1, 2, and 3) with mitral stenosis and auricular fibrillation in comparatively young subjects in which second observations were made. At the second observations, when the patients were considerably improved and the dyspnoea less, the pressures are higher than at the first observation. Cases 8, 9, 10, 11, and 13 belonged to the group with high blood-pressure and arterial disease, and the patients were comparatively advanced in age. At the first observation in Case 8 the general condition had begun to improve, and at the time of the second observation the patient was in an attack of paroxysmal dyspnoea, with a rise of temperature due to the onset of erysipelas, which proved fatal. Case 9 showed a fall in pressure at the second observation, which was made a few hours before death, when the patient was unconscious. The low pressure at the second observation in this case was accompanied by a low carbon dioxide capacity and a pH that was beyond the normal limits on the acid side, and so is not of the same nature as the low pressures seen in the other cases, as will be pointed out later. The second and third observations in Case 11 were made during the improvement in the patient's general condition, but pronounced periodic breathing was present at the first observation, and the blood was drawn mainly during the phase of hyperpnoea. At the second observation slight periodicity was still present, and at the third no periodicity could be recognized. At the first observation in Case 14 the patient had recovered from a severe attack of bronchial asthma and heart failure, and his condition was in striking contrast to that at the time of the later observations when the asthma was severe.

These low carbon dioxide pressures in the arterial blood are associated with figures for the carbon dioxide capacity, as indicated by the content at 40 mm. of Hg, that are within normal limits or slightly below the normal limits, and as the pressure rises with the lessening of the severity of the dyspnoea (Cases 1, 2, and 3)

the capacity rises. With the exception of the second observations in Cases 3 and 9, these low pressures are also associated with figures for the pH that are within normal limits, but usually in the alkaline half of the normal range. This association of low carbon dioxide pressure with pH values in the alkaline half of the normal range points to a condition of increased ventilation due to some stimulus of the respiratory centre other than increased acidity of the blood supplied to the centre, and resulting in a washing out of carbon dioxide from the lungs and the blood. The low normal carbon dioxide capacities would then become explicable on the work of Henderson and Haggard (18), who showed that in the presence of low carbon dioxide pressure a readjustment of available base takes place in such a direction as to maintain the hydrogen-ion concentration at the normal level. Of the two figures for the pH that are outside the normal range, that obtained in the second observation in Case 9 is too acid, which may be explained by the failure of renal function and the retention of non-volatile acids within a few hours of the death of the patient. At the second observation in Case 3, when the dyspnoea was absent and the general condition of the patient greatly improved, the pH is beyond the normal limits to the alkaline side and associated with a pronounced rise in carbon dioxide capacity. No explanation for this exceptional response can be offered.

The cases showing high arterial carbon dioxide pressures include two (Cases 5 and 6) from the group of mitral stenosis and auricular fibrillation. In Case 5 there were signs suggestive of a lesion in the lungs, with pain and friction at the right base in addition to heart failure. The low oxygen content of the arterial blood in this case suggests that the gaseous exchange between the alveolar air and the blood in the lungs was not efficient. In Case 6 a large aneurysmal dilatation of the left auricle complicated the picture. Case 12 had generalized oedema, fluid in the pleural and peritoneal cavities, severe cyanosis of a leaden hue, and deficient oxygen saturation of the arterial blood. At the second observation improvement was well marked and the dyspnoea less, although oedema was still present. At the third observation there was no obvious oedema, and the patient was able to be up. Cases 14 (second admission) and 15 had chronic bronchitis and bronchial asthma in addition to heart failure. These cases with raised arterial carbon dioxide pressure had, therefore, evidence of pulmonary disease in addition to heart failure, or were in the advanced stage of failure with pronounced oedema of the lungs, and in some of them there is evidence of faulty gaseous exchange in the lungs in the low arterial oxygen saturations. In Cases 6 and 14 the raised carbon dioxide pressures are associated with normal oxygen saturations, and this can only be accounted for if there can be a degree of faulty exchange or ventilation sufficient to affect the efficient exchange of carbon dioxide, but not sufficient to affect the saturation of the blood with oxygen. That such a situation can arise is supported by the experimental work of Blalock, Harrison, and Wilson (19) on the effect of obstruction to ventilation, but is opposed by the work of Hastings, Neill, Morgan, and Binger (20) on the gaseous exchange in pneumonia. It is possible that these apparent discrepancies

would disappear if oxygen pressures were estimated throughout, instead of measuring the oxygen in the blood in terms of saturation. In the group of cases with raised carbon dioxide pressures the carbon dioxide content at 40 mm. of Hg is, in general, higher than in the group with low pressures, the figures being in the region of high normal or above the normal range, while the pH is definitely outside the normal on the acid side or in the acid half of the normal range. In these cases, therefore, there is evidence of a carbon dioxide acidosis and an increase in the available base, such as might be expected from the work of Henderson and Haggard to result from carbon dioxide retention.

In the group of observations that showed arterial carbon dioxide pressures within normal limits, the third observation in Case 12 was made at a time when the patient had greatly improved from a condition of severe congestive failure, with oedema of the lungs and fluid in the pleural cavities. It is probable that at this observation the factors operating in the group of cases with high carbon dioxide pressures were present in addition to the factors causing low pressures. Case 7 was in a similar condition at the time of the observation, having recovered from an attack of severe failure with congestion. In Case 17 the patient was suffering from cancer of the uterus as well as from myocardial degeneration, and was in a feeble condition. There were signs of congestion at the bases of the lungs, and the combination of mild pulmonary inefficiency and heart failure may account for the normal carbon dioxide pressure. In Case 4 the dyspnoea was slight. Case 16 was that of a patient with aortic regurgitation, probably rheumatic in origin, and the observation was made during an attack of angina pectoris when the respirations were very irregular and the patient held his breath involuntarily for several seconds at a time. The third observation on Case 2 was made during a second admission for a recurrence of the failure, and the patient died shortly after. At this observation the normal carbon dioxide pressure was accompanied by a carbon dioxide capacity that is below the normal limits. There was considerable oedema of the lungs, which may account for the normal carbon dioxide pressure in spite of the severe dyspnoea, and the low capacity is comparable to the condition found in Case 9 shortly before the death of that patient, when there was evidence of the retention of non-volatile acids. It is possible that this factor was present also in Cases 7 and 12, in which the carbon dioxide capacities are lower than might be expected in the presence of normal or raised carbon dioxide pressures and pH values close to or beyond the normal values on the acid side.

Discussion.

These results indicate that in the absence of such additional factors as pulmonary disease, lesions that occur in the lungs in the severe congestive failure, and the changes in the functions of organs that occur in dying patients, cardiac dyspnoea is associated with a low carbon dioxide pressure in the arterial blood. As the degree of heart failure and the dyspnoea lessens the carbon dioxide pressure rises. This low carbon dioxide pressure is associated with an arterial pH which is in the alkaline half of the normal range, so that an increased acidity

of the blood supplied to the centre cannot be the cause of the increased respiratory activity. The combination of low carbon dioxide pressures, low normal carbon dioxide capacities, and values for the pH in the alkaline half of the normal range is indicative of a dyspnoea due to stimulation of the respiratory centre independent of the character of the blood supplied to the centre. This form of dyspnoea has been discussed by Winterstein (21) and described by him as 'zentrogene'. There is not sufficient evidence at present to decide the nature of this stimulus. Campbell, Hunt, and Poulton suggest that it is due to the increased venosity of the blood in the tissues of the centre due to stasis, and Pearce expresses a similar conclusion. Increased venosity involves two factors, diminished oxygen pressure and raised carbon dioxide pressure. If the stimulus is due to raised carbon dioxide pressure in the tissues it is difficult to account for the low carbon dioxide capacities found in these cases, since the reverse would be expected in accordance with the work of Henderson and Haggard. If the stimulus, therefore, is due to increased venosity it must be the low oxygen tension that accounts for the increased activity of the centre. Cobet suggests that the stimulus in this form of dyspnoea may be the result of some undetermined reflex to the centre. Such a possibility cannot be rejected, but the increasing number of observations on the minute volume of the circulation in heart failure, and the increasing evidence that the minute volume is reduced in the cases with cardiac dyspnoea, suggest that low oxygen pressure in the tissues of the centre is the stimulus that results in this dyspnoea of central origin.

Haldane and Poulton (22) have shown that oxygen deficiency results in an increase of the sensitiveness of the respiratory centre to carbon dioxide and an increase of its activity. This would lead to an increase of the alveolar and arterial oxygen pressures, a reduction of the alveolar and arterial carbon dioxide pressure, and a rise of the pH, unless the latter is obviated by a decrease in the carbon dioxide capacity of the blood. These are precisely the conditions found in this group of cases.

In the cases with raised carbon dioxide pressure in the arterial blood the same stimulus may well be present, since the inability of the lungs to get rid of carbon dioxide would prevent any lowering of the arterial carbon dioxide pressure and mask the effects of the stimulus to the centre. In these cases a further stimulus to the centre is present in the raised carbon dioxide pressure or raised acidity of the blood supplied to the centre.

If, on the other hand, owing to renal inefficiency, there is retention of acid bodies in addition to the condition at the centre which results in low carbon dioxide pressures and pH values in the alkaline half of the normal range, the effects of the latter will be masked to a greater or less extent and the arterial blood will show low carbon dioxide pressures and pH values more acid than normal. In such a case there will be additional stimulus at the centre due to the raised hydrogen-ion concentration of the blood supplied to the centre.

The measurement of the arterial carbon dioxide pressures in cases of cardiac dyspnoea shows, therefore, that this pressure may be normal, may be raised, or

may be lowered beyond the normal limits. The estimations of the oxygen saturation, carbon dioxide capacity, and hydrogen-ion concentration of the arterial blood, and the study of the clinical condition of the patients, in addition to the measurement of the carbon dioxide pressure, point to the presence of a stimulus at the respiratory centre that is probably present in all the cases, and which results in a lowering of the arterial carbon dioxide pressure and in a hydrogen-ion concentration that is in the alkaline half of the normal range. In the presence of pulmonary disease and of the pulmonary lesions associated with severe congestive failure, there is an additional stimulus of the centre due to a raised carbon dioxide pressure and a raised hydrogen-ion concentration in the blood supplied to the centre. In patients shortly before death there may be a retention of non-volatile acids and an additional stimulus of the respiratory centre due to an increased hydrogen-ion concentration in the blood supplied to the centre.

These results are in general agreement with those of Campbell, Hunt, and Poulton, and of Cobet, if the clinical condition of the patients at the time of the observations are taken into consideration.

The significance of the values for the arterial carbon dioxide pressures reported here in the general problem of cardiac dyspnoea has been discussed by one of us in the Goulstonian Lectures (23) of the Royal College of Physicians for 1927.

Summary.

1. A method is described for determining the carbon dioxide pressure of the arterial blood by means of a dissociation curve constructed with arterial blood.

2. This method is liable to sources of error, and the results have been checked by using a second method depending on the construction of a pH-carbon dioxide pressure curve, the pH being determined by the colorimetric method.

3. Thirty observations on the arterial carbon dioxide pressure have been made in seventeen cases of heart failure with dyspnoea.

4. In cases of cardiac dyspnoea the arterial carbon dioxide pressure may be within normal limits or may be below or above these limits.

5. From a consideration of the oxygen saturation, carbon dioxide capacity, and pH of the arterial blood, and of the condition of the patients at the time of observation, it appears that there must be in cardiac dyspnoea a stimulus at the respiratory centre independent of the quality of the blood supplied to the centre, causing increased pulmonary ventilation with a lowering of the carbon dioxide pressure in the arterial blood.

This stimulus may be due to low oxygen tension in the tissues of the centre, the result of lowered minute volume of the circulation.

6. In cases with pulmonary disease in addition to heart failure, or with the pulmonary lesions seen in severe congestive failure, the arterial carbon dioxide pressure is raised. This is the result of inefficient pulmonary ventilation or

inefficient gaseous exchange in the lungs and masks the effects on the arterial blood of the stimulus described above (5). The raised carbon dioxide pressure will act as an additional stimulus to the respiratory centre.

7. In one case examined shortly before death there was evidence of the retention of non-volatile acids, causing an increased hydrogen-ion concentration and low carbon dioxide pressure in the arterial blood. This would mask the effects on the arterial blood of the stimulus described above (5) and act as an additional stimulus to the respiratory centre.

8. In some of the cases with normal arterial carbon dioxide pressure, one or both of the factors described under (6) and (7) were present, in addition to the stimulus described under (5), which is present in all cases of cardiac dyspnoea.

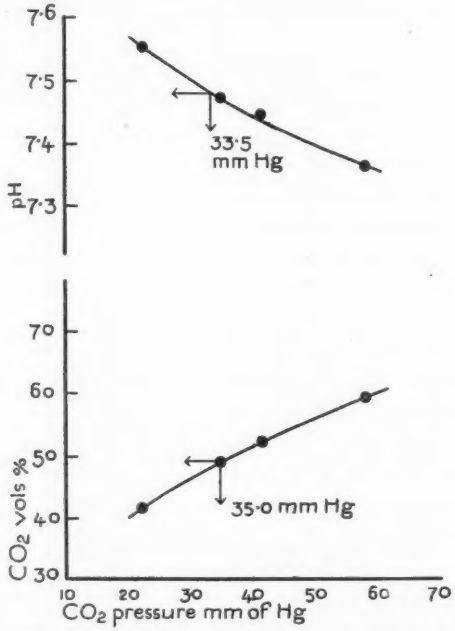
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TABLE I.

Case.	Date.	pH. Colorimetric (uncorrected).	pH. Calculated.	Case.	Date.	pH. Colorimetric (uncorrected).	pH. Calculated.
1	4.1.25	7·46	7·50	8	28.9.25	7·38	7·44
	19.1.25	7·34	7·47		31.11.25	7·45	7·44
2	9.11.25	7·44	7·46	9	24.11.24	7·31	7·36
	7.12.25	7·37	7·42		1.12.24	7·34	7·29
	13.4.26	7·36	7·34	10	5.10.25	7·43	7·52
3	22.12.24	7·47	7·43	13	21.6.26	7·37	7·36
	12.1.25	7·33	7·52	14	29.6.25	7·33	7·48
4	15.12.24	7·48	7·36		22.2.26	7·40	7·27
5	25.1.26	7·40	7·35	16	18.1.26	7·35	7·37
	8.2.26	7·33	7·35	17	12.10.25	7·42	7·38
6	8.12.24	7·38	7·33				



The arrows indicate the arterial point on each curve and the arterial carbon dioxide pressure that corresponds to it.

TABLE II.

Date.	O_2 Capacity.	O_2 Saturation.	CO_2 Capacity at 40 mm. Hg.	CO_2 Content.	CO_2 Pressure. From pH Pressure Curve.	CO_2 Pressure. From Dissociation Curve.	pH. Colorimetric (uncorrected).	pH. Calculated.
	Vols. %.	%.	Vols. %.	Vols. %.	mm.	mm.		
7.2.27	18·3	94	53·2	52·8	40·4	38·8	7·36	7·39
6.2.27	—	—	48·5	47·9	36·5	38·8	7·42	7·34
28.10.27	16·8	96·5	51·6	48·9	33·5	35·0	7·48	7·40

This table gives the values found in the arterial blood of a healthy subject examined on three occasions in a period of eight months.

TABLE III.

Case No.	Age.	Date.	Dyspnoea.	Cyanosis.	Ventricular Rate.	Arterial Blood.							Condition and Remarks.
						O_2 Capacity.	O_2 Saturation.	CO_2 Capacity at 40 mm. Hg.	CO_2 Content.	CO_2 pressure. From pH (color.) Pressure Curve.	CO_2 pressure. From Dissociation Curve.	pH (calculated).	
						Vols. %.	%.	Vols. %.	Vols. %.	mm.	mm.		
1	43	4.1.25	+ + +	+ +	150	16·4	98	45	33·6	17	21	7·50	Mitral stenosis and auricular fibrillation.
		19.1.25	+	+	76	17·5	98	50	43·4	29	29	7·47	Improved.
2	27	9.11.25	+ +	+	60	18·4	97	46	41·4	31	28	7·46	Mitral stenosis, aortic regurgitation. Digitalis intoxication.
		7.12.25	+	+	76	17·2	96	47	43·2	31	32	7·42	Improved.
		13.4.26	+ +	+	76	17·9	97	42	39·9	35	35	7·34	Readmission. Died one month later.
3	25	22.12.24	+ +	sl.	116	17·7	97	46	42·9	26	31	7·43	Mitral stenosis, aortic regurgitation, and auricular fibrillation.
		12.1.25	–	–	70	16·9	97	59	55·6	31	33	7·52	Rhythm regular following quinidine.
4	35	15.12.24	+	+	90	17·25	98	44	42·2	30	36	7·36	Mitral stenosis, aortic regurgitation, and auricular fibrillation. Much improved since admission.
5	34	25.1.26	+ +	+	70	14·4	92	53	55·2	42	47	7·35	Mitral stenosis, aortic regurgitation, and auricular fibrillation. Pulmonary lesions in addition.
		8.2.26	+ +	+	72	15·8	84	52	56·0	42	48	7·35	Acute pain in right thorax; ? infarct.

TABLE III (*continued*).

Case No.	Age.	Date.	Dyspnoea.	Cyanosis.	Ventricular Rate.	Arterial Blood.							Condition and Remarks.
						O_2 Capacity.	O_2 Saturation.	CO_2 Capacity at 40 mm. Hg.	CO_2 Content.	CO_2 Pressure. From pH (color.) Pressure Curve.	CO_2 Pressure. From Dissociation Curve.	pH (calculated).	
						Vols. %.	%.	Vols. %.	Vols. %.	mm.	mm.		
6	26	8.12.24	sl.	sl.	64	14·0	100	48	51·4	42	45	7·33	Mitral stenosis, auricular fibrillation. Aneurysmal dilatation of left auricle.
7	67	16.6.24	+	+	76	21·2	93·8	42	40·8	38	39	7·32	Mitral stenosis, auricular fibrillation. Much improved since admission.
8	60	28.9.25	+	–	80	17·3	96	49	43·7	29	31	7·44	Myocardial degeneration, arterio-sclerosis. Improving.
		31.11.25	+ +	–	108	13·8	96	49	44·9	30	31	7·44	Dyspnoea and fever with onset of erysipelas.
9	70	24.11.24	+	–	75	17·5	98	43	38·8	31	33	7·36	Myocardial degeneration, arterio-sclerosis. Improving.
		1.12.24	+	+	100	18·3	91	31	27·6	27	27	7·29	Unconscious, dying.
10	61	5.10.25	+	–	75	18·0	95	48	39·2	24	24	7·52	Myocardial degeneration, chronic gout, arterio-sclerosis, paroxysmal dyspnoea.
11	58	11.2.24	+	sl.	64	16·8	100	44	39·9	30	30	7·42	Myocardial degeneration, chronic interstitial nephritis. Cheyne-Stokes's breathing. Blood drawn during hyperpnoea.
		25.2.24	+	–	75	18·0	96	43	37·1	28	29	7·41	Slight periodicity.
		17.3.24	sl.	–	58	16·7	97·7	45	38·8	29	28	7·44	Respirations regular.

12	53	28.1.24	+ + +	+ +	80	17·3	88	42	45·1	41	47	7·26	Myocardial degeneration. B.P. 230–150. Severe oedema, ascites, fluid in pleural cavities, pulmonary congestion.
		3.3.24	+ +	+	84	21·0	87	46	51·8	53	51	7·31	Improved. Still oedematous.
		31.3.24	+	sl.	88	18·0	99	46	44·0	32	36	7·39	Much improved, no oedema.
13	48	21.6.26	+	+	90	14·4	91	43	39·0	35	32	7·36	Myocardial degeneration, chronic interstitial nephritis. Slight oedema.
14	51	29.6.25	+	sl.	75	19·8	100	53	49·6	28	33	7·48	Aortic regurgitation. Chronic bronchitis and asthma. Slight oedema. Much improved.
		15.2.26	+ + +	+	96	19·3	100	44	47·8	40	54 [1]	7·23 [1]	Readmission. Severe dyspnoea and oedema.
		22.2.26	+	sl.	84	19·8	96	47	50·5	42	47	7·27	Improving.
15	35	9.10.25	+ +	+ +	80	19·4	91	59	66·9	70 [1]	70 [1]	7·26 [1]	Chronic bronchitis. Fibrosis of lung.
16	56	8.1.26	+	sl.	92	16·3	96	48	47·3	34	39	7·37	Aortic regurgitation during attack of angina pectoris.
17	65	12.10.25	sl.	–	70	14·3	92	51	51·4	39	41	7·38	Carcinoma of uterus. Numerous extra-systoles. Slight oedema.

[1] By extrapolation.

Case Reports.

Case I. M. G., female, aged 43; six children.

Heart failure, mitral stenosis, auricular fibrillation. No history of rheumatism. October 1920, sudden onset of abdominal pain and shortness of breath. Never well since; auricular fibrillation noted at this time. Successive attacks of congestive failure with oedema, usually due to failure to take digitalis. Had been in hospital on several occasions. Admitted January 1, 1925: orthopnoea, malar flush, cyanosis. Heart: apical impulse diffuse and feeble, left border $5\frac{1}{4}$" from mid-line in sixth space, enlarged to right, auricular fibrillation, ventricular rate 160, no radial pulse. Lungs: a few râles at bases, respirations 28. Abdomen: liver enlarged and tender. Oedema of legs. Urine: 1008, albumin a trace.

January 4, 1925. Little change with rest in bed. Ventricular rate 150, no radial pulse. Respirations 28.

January 19, 1925. Improved on digitalis. No oedema, liver smaller, dyspnoea less, still orthopnoeic. Ventricular rate 76, no deficit.

Case II. E. B., female, aged 27. Heart failure, mitral stenosis, auricular fibrillation. No history of rheumatic fever. 1924, during pregnancy increasing dyspnoea. After birth of child January 1925, cyanosis, dyspnoea worse, and swelling of ankles. May 1925, mitral stenosis diagnosed. Admitted November 7, 1925: digitalis intoxication, orthopnoea, cyanosis, malar flush. Vomiting. Heart: coupled rhythm, rate 80, radial pulse 40, apical impulse diffuse, heaving, left border 6" from mid-line in sixth space, enlarged to right, murmurs of mitral stenosis and tricuspid regurgitation. Lungs: few râles at bases after coughing; respirations 28, laboured. Abdomen: liver greatly enlarged, no ascites. Slight oedema of lumbar back and ankles. Urine: 1024, albumin a trace.

December 7, 1925. Dyspnoea and orthopnoea less. Liver much smaller. Is getting up. Ventricular rate 76, no pulse deficit. Discharged December 20, 1925.

April 6, 1926. Readmitted. Severe orthopnoea and dyspnoea. Marked oedema of legs and lumbar back. Liver greatly enlarged. Coughing up blood-stained sputum, fluid in right pleural cavity. Ventricular rate 80, no deficit. Very little improvement and died a few days after discharge on May 23, 1926.

Case III. B. T. B., male, aged 25; war pensioner. Heart failure, mitral stenosis and aortic regurgitation, auricular fibrillation. Rheumatic fever during war. A few weeks before admission, sudden onset of dyspnoea. Admitted December 18, 1924: orthopnoea, no cyanosis. Heart: no evidence of enlargement, murmurs of mitral stenosis and aortic regurgitation, auricular fibrillation, ventricular rate 130, radial pulse 100. Lungs: respirations 38, rapid and shallow, sibili and râles at bases. Abdomen: liver enlarged. Urine: albumin a trace. No oedema.

December 22, 1924. Improved, has lost fluid. Ventricular rate 116, radial pulse 82, respirations 24.

January 12, 1925. No evidence of heart failure. Normal rhythm following quinidine. No dyspnoea. Liver still easily palpable. Pulse-rate 70; respirations 16.

Case IV. F. B., female, aged 35, three children. Heart failure, mitral stenosis, aortic regurgitation, auricular fibrillation. 1906, acute rheumatism; dyspnoea on exertion since. 1922, swelling of ankles, and in bed off and on since. Admitted December 9, 1924: dyspnoea and orthopnoea, slight cyanosis, malar flush. Heart: diffuse impulse, left border $5\frac{1}{2}$" from mid-line in fifth space, murmurs of mitral stenosis and aortic regurgitation; ventricular rate 180, radial pulse 170. Lungs: respirations 40; few râles at both bases. Abdomen: liver greatly

enlarged, some ascites. Oedema of legs and lumbar back. Urine: 1015, albumin present.

December 15, 1924. Considerable improvement; dyspnoea and oedema less; respirations 25; ventricular rate 90, no pulse deficit.

Case V. J. L., male, aged 34, clerk. Heart failure, mitral stenosis, aortic regurgitation, auricular fibrillation, pleurisy. 1908, rheumatic fever, since then dyspnoea and cough. Increasing disability and palpitations. June 1925, swelling of feet; November 1925, dyspnoea severe. Admitted December 12, 1925; acute pain in right thorax, cyanosis, orthopnoea. Heart: apical impulse diffuse and forcible, left border 7″ from mid-line in seventh space, murmurs of aortic regurgitation and mitral stenosis, auricular fibrillation, ventricular rate 120. Lungs: râles and impaired percussion at both bases, especially right, friction left axilla, respirations 30, lower thorax not expanding. Abdomen: liver enlarged, spleen just palpable. Urine: albumin a trace, R.B.C., W.B.C. No oedema. Blood cultures negative.

January 25, 1926. Improved, still cyanosis and orthopnoea, ventricular rate 70, respirations 24.

February 8, 1926. Dyspnoea more marked. Pain in right axilla, friction and impaired percussion, suggesting infarct.

Case VI. L. L., female, aged 26, two children. Heart failure, aortic regurgitation and mitral stenosis, aneurysmal dilatation of left auricle, auricular fibrillation. 1908, rheumatic fever. 1920, after birth of child, acute onset of dyspnoea and oedema. Following this had two attacks of congestive failure, and between attacks dyspnoea on exertion. Admitted November 23, 1924; marked dyspnoea and orthopnoea, cyanosis, and malar flush. Heart: diffuse heaving apical impulse, left border 6″ from mid-line in seventh space, greatly enlarged to right due to aneurysmal dilatation of left auricle, murmurs of aortic regurgitation and mitral stenosis, auricular fibrillation, ventricular rate 120, radial pulse 110. Lungs: lower thorax retracted on inspiration, few râles at bases, respirations 35. Abdomen: liver enlarged. Urine: 1032, no albumin, no casts. No oedema.

December 12, 1924. Much improved, no orthopnoea, slight dyspnoea and cyanosis, ventricular rate 64, no pulse deficit.

Case VII. E. K., female, aged 67; five children. Heart failure, mitral stenosis, auricular fibrillation. No history of rheumatic fever. 1923, dyspnoea and palpitations. Gradual increase of dyspnoea and onset of oedema of legs. Admitted May 31, 1924: orthopnoea and cyanosis. Heart: impulse beneath sternum, left border 5½″ from mid-line in fifth space, enlarged to right; murmurs of mitral regurgitation and stenosis, auricular fibrillation, ventricular rate 160, no radial pulse. Lungs: râles at bases. Abdomen: very fat, ascites, liver enlarged. Oedema of lumbar back and legs. Urine: albumin present, no casts.

June 16, 1924. Much improved. Still some oedema, orthopnoea, and cyanosis. Ventricular rate 76, no pulse deficit.

Case VIII. W. H. C., male, aged 60; Post Office clerk. Heart failure, myocardial degeneration, arterio-sclerosis. 1928, attacks of precordial pain and dyspnoea. These increased in frequency. August 1925, severe attack and confined to bed since. Admitted September 10, 1925: cyanosis, orthopnoea, mentally sluggish, fearful of attacks, dyspnoea severe on least exertion. Heart: impulse diffuse, left border 5″ from mid-line in sixth space, loud rough systolic murmur at apex, extra-systoles and pulsus alternans, rate 120. Electrocardiogram shows lesion of right bundle branch. Blood-pressure: systolic 155, diastolic 100. Lungs: emphysema, respiration 30. Abdomen: some free fluid, liver not enlarged. Oedema of legs and lumbar back. Urine: 1022, albumin a trace. Radial artery irregularly thickened.

September 28, 1925. Improved, oedema less. Pulse 80, respirations 20. Pulsus alternans not present.

November 3, 1925. Attack of dyspnoea and pain when blood taken. Cyanosis pronounced. Temperature 100° F.; pulse 108; respirations 20. This was onset of fatal attack of erysipelas.

Case IX. L. J. N., male, aged 70; waiter. Heart failure, myocardial degeneration, arterio-sclerosis. 1922, occasional shortness of breath and swelling of ankles. July 1924, swelling of abdomen and severe dyspnoea. Admitted October 21, 1924: pale, with dilated venules on face, orthopnoea and Cheyne-Stokes's breathing. Heart: apical impulse thrusting but diffuse, left border 5″ from mid-line in fifth space, enlarged to right, soft systolic murmur in all areas, numerous ventricular premature beats, rate 80–90. Lungs: scattered rhonchi and râles, especially at bases; emphysema; respirations 40. Abdomen: ascites, liver and spleen enlarged. Oedema of abdominal wall, lumbar back and thighs. Radial artery irregularly thickened. Blood-pressure: systolic 170, diastolic 100. Urine: 1018, albumin 1·0 per cent., hyaline and granular casts, few R.B.C. Blood urea: 0·033 per cent.

November 24, 1924. Much improved, no periodic breathing; dyspnoea, orthopnoea, and oedema less. Pulse 75; respirations 24.

December 1, 1924. Unconscious, dying. Cyanosed. Pulse 100; respirations 55.

Case X. E. B., male, aged 61, builder. Heart failure, myocardial degeneration, right bundle branch block, chronic gout. 1923, attack of paroxysmal dyspnoea with sense of pressure in thorax; attacks increasing in frequency, occasional bronchitis. Admitted September 29, 1925: no orthopnoea nor cyanosis, no dyspnoea when in bed. Heart: no enlargement found, first sound feeble, second aortic accentuated, rate 64; electrocardiogram shows right bundle branch block. Blood-pressure: systolic 175, diastolic 120. Lungs: emphysema, a few râles at bases. Abdomen: liver enlarged. Urine: natural.

October 3, 1925. Attack of paroxysmal dyspnoea in night, heart-rate 156, followed by much sputum, blood-stained tenacious mucus. During attack liver tender and larger.

October 5, 1925. Not so comfortable since attack, slight dyspnoea, otherwise condition as on admission.

Case XI. A. G., male, aged 58, printer. Heart failure, myocardial degeneration, arterio-sclerosis, chronic interstitial nephritis. In 1922, increased frequency of micturition noted. December 1923, swelling of feet commenced and one month later shortness of breath and cough. Admitted February 2, 1924: severe dyspnoea and orthopnoea, Cheyne-Stokes's breathing, slight cyanosis of lips. Heart: apical impulse diffuse, left border 7″ from mid-line in sixth space, heavy first sound at apex, second aortic sound accentuated, occasional extra-systoles, no evidence of valvular disease. Rate 90. Blood-pressure: systolic 290, diastolic 178. Lungs: lower thorax drawn in on inspiration, emphysema, scattered sibilant rhonchi. Abdomen: no ascites, liver 1″ below costal margin. Urine: 1010; albumin a trace, sugar a trace, R.B.C., W.B.C., hyaline and granular casts. Considerable oedema of legs. Retinal and radial arteries thickened and tortuous, scattered retinal exudate. Blood urea: 0·055 per cent.

February 25, 1924. Dyspnoea less, still slight periodicity present. Pulse-rate 70–80.

March 17, 1924. Much improved, no periodicity in respiratory rhythm, no oedema. Pulse-rate 50–60.

Case XII. H. D., female, aged 53; four children. Heart failure, ascites, myocardial degeneration, raised blood-pressure. July 1923, swelling of legs.

December 1923, rapidly increasing swelling of abdomen with dyspnoea and cyanosis. Admitted January 13, 1924: orthopnoea, deep cyanosis. Heart: diffuse slapping apical impulse, left border 6″ from mid-line in sixth space, no evidence of valvular disease, rate 120, occasional extra-systoles. Blood-pressure: systolic 230, diastolic 150. Lungs: lower thorax fixed, congestion and oedema both bases, fluid in pleural cavities, emphysema, respirations 24. Abdomen: greatly distended, ascites. Gross oedema of legs, hands, and lumbar back. Urine: 1010, albumin 0·3 per cent., W.B.C., R.B.C., hyaline and granular casts.

January 28, 1924. Improved, cyanosis and oedema less. Pulse 70–80.

March 3, 1924. Oedema much less, still râles at both bases. Blood-pressure: systolic 200, diastolic 100.

March 31, 1924. Is getting up. Slight cyanosis, no oedema. Pulse 88; respirations 24. Blood-pressure: systolic 190, diastolic 100. Still some râles at bases.

Case XIII. A. G., female, aged 48; six children. Heart failure, myocardial degeneration, chronic interstitial nephritis. 1924, fainting and precordial pain. 1925, hemiplegia, recovered. May 1926, palpitations, dyspnoea, orthopnoea, attacks of nocturnal dyspnoea. Admitted June 14, 1926: pale, slight cyanosis, severe dyspnoea on least exertion. Heart: impulse localized and heaving, left border 5¼″ from mid-line in fifth space, ringing second sound at aortic base, rate 90. Blood-pressure: systolic 260, diastolic 150. Lungs: a few scattered râles. Abdomen: liver greatly enlarged. Oedema of legs and lumbar back. Radial and retinal arteries thickened, retinal exudate and haemorrhages. Urine: 1010, albumin 0·1 per cent., W.B.C., and granular casts. Blood urea: 0·060 per cent.

June 21, 1926. Dyspnoea at rest. Pulse 90; respirations 35. (Died August 3, 1926, in uraemia.)

Case XIV. M. V., male, aged 51, publican. Heart failure, aortic regurgitation, myocardial degeneration, chronic bronchitis and asthma. Since 1916 bronchitis and asthma each winter. Since December 1924 attacks more frequent and dyspnoea constant. May 1925, oedema of feet and palpitations. Admitted June 3, 1925: pale, slight cyanosis, orthopnoea. Heart: apical impulse heaving, left border 4″ from mid-line in fifth space, aortic regurgitation, rate 90. Blood-pressure: systolic 130, diastolic 80. Lungs: wheezing respirations, lower thorax retracted on inspiration, rhonchi and sibili all over, respirations 32. Abdomen: liver greatly enlarged, ascites. Oedema of legs. Urine: 1020, albumin a trace, no blood, no casts. Wassermann negative. Electrocardiogram shows right bundle branch lesion.

June 29, 1925. Much improved. Respirations 20. Orthopnoea still present. Pulse 75. No oedema.

Readmitted February 11, 1926, condition as on previous admission.

February 15, 1926. Dyspnoea and orthopnoea severe. Respirations laboured and lower thorax retracted on inspiration. Signs of asthma. Râles at bases. Pulse 96; respirations 30.

February 22, 1926. Improved. Oedema less. Pul se 84 Respirations 24, and less laboured.

Case XV. F. W., male, aged 35, painter. Heart failure, fibrosis of lung, chronic bronchitis and emphysema. During war had attacks of dyspnoea from fumes in munition factory. Since November 1923 dyspnoea on exertion, cough and muco-purulent sputum, at times orthopnoea.

Admitted October 16, 1925: Laboured breathing, orthopnoea, pronounced cyanosis. Heart: generalized heaving impulse, left border 3½″ from mid-line in sixth space, enlarged to right, rate 90–100, regular. Blood-pressure: systolic 105, diastolic 54. Lungs: respirations 28, inspiratory recession of intercostal spaces, emphysema, rhonchi all over, scattered râles, numerous at bases, evidence of fibrosis. Abdomen: liver enlarged. Fingers clubbed. No tubercle bacilli found.

October 19, 1925. Improved with oxygen administration. Pulse 80; respirations 16. Blood-pressure: systolic 105, diastolic 70. Oxygen administration stopped one hour before blood taken.

Case XVI. E. M., male, aged 56, actor. Aortic regurgitation, angina pectoris. Three attacks of rheumatic fever between 1880 and 1900. Angina pectoris since 1921. Since 1924 dyspnoea on exertion and swelling of feet. Admitted January 18, 1926: in attack of angina, orthopnoea, cyanosis, in great pain, sweating, pallor. Heart: apical impulse heaving, left border 5¼″ from mid-line in fifth space, aortic regurgitation, rate 92. Blood-pressure: systolic 165, diastolic 55. Lungs: holds breath for several seconds when pain severe, râles at bases. Urine: 1020, albumin a trace. Wassermann negative.

Case XVII. A. M., female, aged 65, lady's-maid. Heart failure, myocardial degeneration, carcinoma of cervix. May 1925, dyspnoea, pain in praecordium, palpitations. Admitted October 3, 1925: appears tired, no cyanosis, no orthopnoea, dyspnoea slight. Heart: impulse feeble, left border 5″ from mid-line in fifth space, soft systolic murmur at apex, frequent extra-systoles, pulsus alternans, rate 70–80. Lungs: râles at bases after coughing. Urine: pus cells and staphylococci. No oedema. Carcinoma of uterine cervix.

EVIDENCE, DRAWN FROM A STUDY OF THE THERAPEUTICS OF GRAVES' DISEASE, OF TWO FUNCTIONS IN THE THYROID PHYSIOLOGY[1]

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With Plates 1 and 2

Two well-defined histological events occur in the thyroid gland. They have been recognized as normal events in the thyroid since 1883 (Hürthle (11), Langendorff (13), Biondi (4)), and more recently, Aschoff (2 and 3), de Quervain (17), Cooper (6), Drennan (7). These events are the storage of 'colloid' and the production of 'secretion proper', i.e. Hürthle's *Hauptsecretion* (Williamson and Pearse (23)). The secretion proper of the thyroid gland is not iodo-colloid nor thyroxin, but is an iodine-free material produced in the non-colloid or hyperplastic areas which constitute the bulk of the gland in Graves' disease and the whole of the gland in adenoid goitre.

As evidence accumulates, the conception is gaining ground that these two events are best studied as two distinct functions. The chemistry of secretion is not that of iodo-colloid (Williamson and Pearse (26)). The biological effect of secretion is not that of iodo-colloid (Wegelin and Abelin (22); Williamson, Pearse, and Cunnington (27)). The conditions as to the pH governing the production of secretion are not those under which iodo-colloid is produced (Troell (20), and Troell and Josephson (21)). The physiological effect of thyroxin or pure iodo-colloid is not that of whole gland substance (Asher (1), de Quervain (18), Oswald (15)). These and other clinical and pathological observations suggest that the thyroid gland has a dual function represented in the tissue by (1) the storage of iodo-colloid, and (2) the production of secretion proper.

Iodo-colloid and secretion have been confused in the effort to explain Graves' disease as a hyperthyroidism or a dysthyroidism. The two entities have been related as cause and effect: either the secretion is postulated as the mother substance of iodo-colloid or the iodo-colloid as the mother substance of secretion. The same facts are used to maintain both views.

It has already been shown that the evidence gathered from anatomical, pathological, or physiological studies does not support either of these theories.

[1] Received June 8, 1928.

The theories were based on the effect of therapeutic measures (medical, e. g. iodine therapy; or surgical, e. g. amputation of the goitre) on the tissue of the goitre.

The facts drawn from a study of the effects of therapeutic measures on the gland which are presented in this communication support the conception of a dual function in the thyroid physiology. They throw some light on the part played by each function in the symptomology of Graves' disease.

Methods of Treatment.

There are many methods of treating Graves' disease. This report is concerned only with material taken from cases treated in two different ways:

1. Partial removal of the thyroid gland from cases of Graves' disease in which iodine treatment was *carefully excluded*. There are 403 cases included in this category, which, for convenience, will be called the *non-iodized* group.

2. Partial removal of the thyroid gland from cases of Graves' disease in which pre-operative iodine treatment was *consistently* used. This group, consisting of 104 cases, will be called the *iodized* group.

It is to be understood that only those cases are included for which operation was deemed necessary. There is probably another category of cases which do not fall within the scope of surgery, but with these cases this study is not concerned.

Nature of Material under Investigation.

In studying Graves' disease from any point of view it is necessary to select the material with the greatest care. There are two main reasons for this. The first is that the term Graves' disease covers a very wide group of clinical conditions. In particular it now includes thyrotoxicosis with exophthalmos and thyrotoxicosis without exophthalmos. Since both forms of intoxication are relieved by amputation of sufficient thyroid gland tissue, they are considered as quantitative or qualitative variations of the same underlying conditions. In this study are included only thyroid glands taken from cases of Graves' disease with the full clinical syndrome: exophthalmos, persistent tachycardia, tremor, wasting, and smooth goitre. (Cases with obvious nodular goitre are excluded.)

The second reason for careful selection is that the cases cannot be grouped according to the pathological conditions found in the thyroid gland. Graves' disease, though manifestly associated with the thyroid gland, has no typical goitre even when the cases are carefully selected.

There is, however, one feature common to all thyroid glands in Graves' disease. It is their very manifest 'secretory activity'. The secretory activity may occur in diffuse or circumscribed areas scattered throughout the gland. These areas may be large or small, many or few. There may be, alongside the secretory areas, abundant iodo-colloid. On the other hand, iodo-colloid may have

entirely disappeared from the gland, leaving a non-colloid goitre. This latter, in our experience, never occurs apart from Graves' disease. *It is the only non-colloid goitre.* For this reason we have called it 'adenoid goitre',[2] considering it convenient to separate it from all other goitres for purposes of subsequent study (Williamson and Pearse (24)).

Adenoid goitre is not an empty resting thyroid like the gland in starvation; it is a very active secreting gland. For this reason it has been looked upon as a 'hyperplastic' goitre. It is not necessarily active in every follicle, for rest tissue or 'empty' follicles may be scattered throughout its substance. It contains in the active follicles an abundance of 'secretion proper'. This secreting tissue has already been shown (Williamson, Pearse, and Cunnington (27)) to be biologically inactive when tested on tadpoles, and the secretion itself has been shown to contain no iodine. Moreover, when the tissue of the adenoid goitre contained iodine, which it did in only 6 per cent. of samples, this iodine was biologically inactive. Now even traces of iodo-colloid contain iodine and are biologically active. Thus, adenoid goitre is justly described as a non-colloid goitre.

Furthermore, in the other glands associated with Graves' disease included in this study, where the gland was not of the homogeneous consistency of adenoid goitre but presented scattered nodes or patches of secreting tissue, these secretory areas were found to possess the same characteristics as the secreting tissue of adenoid goitre. Indeed, wherever it be found, in adenoid goitre, in the scattered areas of other glands associated with Graves' disease, or in the normal gland itself, secreting tissue gives the same reaction to histological, chemical, and biological tests alike.

It will be evident that adenoid goitre, a non-colloid goitre, with these well-defined positive characters, provides a means of gauging the effect of treatment on the *iodo-colloid function* of the thyroid gland in cases of Graves' disease.

I. *Results in the Non-iodized Group.*

There are two features of this group that call for attention:

(a) *The incidence of adenoid goitre.* In the non-iodized group 193 adenoid goitres occurred in the 403 cases; an incidence of 48 per cent.

The tissue removed in the 193 glands contained no colloid.[3] The secretion within the follicles contained no iodine. The whole tissue had no biological effect on tadpoles. The macroscopic appearance of these goitres was equally characteristic (Pl. 1, Fig. 1).

We may conclude that a characteristic goitre, adenoid goitre, devoid of thyroxin, occurs in 48 per cent. of cases of Graves' disease when *iodine treatment is excluded.*

[2] *Adenos* = glandlike (e.g. pancreas, salivary).

[3] By this it is not implied that the follicles were 'empty'; they contained *secretion* but not colloid. (See Williamson and Pearse (23).)

(b) *The effect of surgical treatment on the residue of the gland in the non-iodized group.* We were fortunate in encountering 33 out of 403 cases untreated with iodine in which the operation proceeded in two or three stages.

First operation: in 28 of the 33 cases the first operation yielded material which contained no colloid (i. e. adenoid goitre.) The biological and chemical characters of this tissue were examined according to the methods already published.[4] In 23 cases the goitre tissue was submitted to the tadpole test. Samples of tissue with well-filled alveoli were found to be biologically inactive when tadpoles were fed with it. Moreover, in 16 out of the 23 cases tested no iodine could be detected in the samples. Any iodine present (7 cases, Table I) was inactive and had not the effect of thyroxin when tested on tadpoles. The whole tissue behaved like tissue taken from the other adenoid goitres, or like 'secreting tissue' from normal glands.

Now, the material removed at operation included tissue from one or both lobes and the isthmus. It is not conceivable that the surgeon removed *only* that part of the goitre which did *not* contain iodine. The tissue must be taken to have been a fair sample of the whole goitre, and any differences between material taken from the gland at the first operation and that removed at the second operation can reasonably be regarded as the effect of removal of secreting tissue.

Second operation: all the material received from the 28 cases after the second operation (time elapsed, 8 days to 3 weeks) showed a very striking change. The portions of the glands removed at the second operation all contained *iodo-colloid tissue* as well as secretion tissue. The amount of each type of tissue varied through the widest limits.

TABLE I.

Non-Iodized Group.

	Secreting Tissue.				*Colloid Tissue.*	
	First Operation.		Second Operation.		Second Operation.	
	Iodine.	Tadpole.	Iodine.	Tadpole.	Iodine.	Tadpole.
1	Nil	Nil	0·009	Nil	0·47	Positive
2	0·06	Nil	Nil	Nil	—	—
3	0·019	Nil	Nil	Nil	—	—
4	0·049	Nil	Nil	Nil	0·077	Positive
5	0·006	Nil	Nil	Nil	—	—
6	0·017	Nil	Nil	Nil	0·094	Positive
7	Nil	Nil	Nil	Nil	—	—
8	0·008	Nil	0·011	Nil	0·76	Positive
9	Nil	Nil	—	—	0·38	Positive
10	0·014	Nil	—	—	0·079	Positive
11	Nil	Nil	—	—	0·086	Positive

In seven cases the colloid tissue was tested and found to contain iodine and to be biologically *active* (Table I). But secreting tissue, with laden alveoli, from eight cases was found to be biologically inactive in spite of the fact that two of the samples contained iodine (Table I). Both the iodo-colloid tissue and the

[4] For methods employed in these tests, see Williamson, Pearse, and Cunnington (27).

secreting tissue, therefore, had all the characters found in the normal glands. No iodine was administered in the interim. From this it must be inferred that the iodine necessary for this change was *in the body* at the time of the first operation, and that by means of the first operation, in some manner at present unknown, it had been released and made available for storage within the gland.

The important fact to note is that removal of some of the secreting tissue enabled iodo-colloid to reappear in the gland. This must mean that an excess of secreting tissue operates as an inhibitory factor preventing the storage of iodo-colloid in the thyroid.

II. *Results in the Iodized Group.*

In this group we have to note:

(a) *The effect of iodine on the incidence of adenoid goitre in Graves' disease.* From among the cases in which pre-operative treatment with iodine was the rule, out of 104 glands received from the surgeons, there were two adenoid goitres only. Clinically the disease showed the same symptoms to the same degree. Adenoid goitres occurred in 48 per cent. of cases in the non-iodized group. There were but *2* cases in *104* in the iodized group.

Iodine treatment, then, practically abolishes adenoid goitre from among the goitres of Graves' disease.[5] This therapeutic effect of iodine is well known; it was the reason for Plummer's advocacy of iodine treatment as a pre-operative measure in Graves' disease.

(b) *The effect of iodine on the secreting tissue and on the iodo-colloid tissue.* In the morphology of the gland a change occurred following iodine administration. This was first noted by Marine and Lenhart (14). It is the experience of all workers.

Iodine-treated goitre contained *both* secreting tissue and iodo-colloid tissue. The amount of stored iodo-colloid appearing in the goitre was macroscopic or microscopic. The quantity of iodo-colloid stored bore no relation to the amount of iodine ingested (Pl. 1 and 2, Figs. 2 to 6). Indeed in two cases, in spite of intensive feeding with iodine, no iodo-colloid appeared.

Nor was it apparent that iodine feeding reduced the actual amount of *active* secreting tissue. In these cases the amount of secreting tissue varied as widely as the amount of iodo-colloid tissue (Pl. 1 and 2, Figs. 2 to 6). There was no evidence of inhibition of active secretion.

A point to decide was the effect of iodine on the properties of the goitre tissue. Had the nature of the secretion in the active secreting areas changed as the result of the iodine treatment? Was the iodo-colloid normal and physiologically active?

[5] The goitre following iodine treatment is the hypertrophic goitre (Williamson and Pearse (24)), the diffuse adenomatosis of Goetsch (8), the diffuse hyperplasia of others, the struma parenchymatosa et colloides diffusa of the continental workers.

Areas of active secreting tissue were separated from colloid areas by the method already described (Williamson, Pearse, and Cunnington (27)). Samples of secreting tissue from nine glands were studied. The nine samples of secreting tissue, all with well-filled follicles, proved to be biologically inactive when given to tadpoles (Pl. 2, Figs. 7 and 8). Moreover, in seven of the nine samples of secreting tissue no trace of iodine could be detected (Table II). The secretion in the secreting tissue still retained its normal characters in spite of the iodine treatment.

TABLE II.

Iodized Group.

	Secreting Tissue.		*Colloid Tissue.*	
	I_2%.	Tadpole.	I_2%.	Tadpole.
1	Nil	Nil	0·377	Positive
2	0·008	Nil	—	—
3	Nil	Nil	0·441	Positive
4	—	—	0·165	Positive
5	Nil	Nil	0·74	Positive
6	—	—	0·265	Positive
7	Nil	Nil	—	—
8	—	—	0·305	Positive
9	Nil	Nil	—	—
10	—	—	0·483	Positive
11	Nil	Nil	—	—
12	0·03	Nil	0·73	Positive
13	—	—	0·61	Positive
14	—	—	0·33	Positive
15	Nil	Nil	—	—
16	—	—	0·56	Positive

Colloid was selected from eleven goitres of the iodine treated cases. In every case it contained iodine and was very active on tadpoles (Pl. 2, Figs. 7 and 8, and Table II). The colloid, appearing after iodine treatment, conformed to what is known of normal colloid.

The effect of iodine treatment, thus, was to provide, in a primarily *non-colloid* gland, a store of normal iodo-colloid; it did not inhibit secretory activity *nor had it permanently affected the symptoms* of the disease.

In the iodine group one other effect of treatment is to be noted. Three cases were encountered in which the symptoms seemed to be due entirely to the material absorbed from *solitary* circumscribed areas of secreting tissue. These areas of lobular hyperplasia are commonly called 'adenomas'—a somewhat unfortunate name, since they do not represent neoplastic growth [6] (see also Reinhoff and Lewis (19)). The cases appeared to be simple cases of Graves' disease with full syndrome and a smooth goitre. At operation one well-defined circumscribed swelling presented in the body of each gland. The part removed weighed (1) 9·0 grm., (2) 7·6 grm., (3) 3·9 grm. respectively. The histology of these nodes was that of adenoid goitre: that is to say, it gave a uniform picture of secreting tissue. In one case the small node was analysed and proved to

[6] Their correct description is 'circumscribed lobular hyperplasia'.

contain no iodine. In a second the tissue was given to tadpoles and produced no result. (See also Graham (9); Wegelin and Abelin (22).) No analysis of the third tissue was possible. In each case the symptoms disappeared and the subsequent history of the case was similar to that of the other cases of Graves' disease. Thus, the intoxication can only have arisen from the areas of tissue removed, from the secreting tissue in fact.

Discussion.

This study of the effects of certain forms of treatment upon the gland in Graves' disease gives emphasis to the following facts:—1. Secretory activity is the significant feature of the thyroid gland in Graves' disease. 2. Iodo-colloid disappears from the thyroid gland in 48 per cent. of cases of Graves' disease. 3. Feeding with iodine causes iodo-colloid to reappear in the gland. 4. The iodo-colloid which reappears is normal, active iodo-colloid; i.e. it acts like thyroxin when tested biologically. 5. Iodine feeding does not permanently affect the symptoms of the disease. 6. Feeding with iodine does not abolish the secretory activity in the thyroid gland. 7. The partial removal of pure secreting tissue results in the return of normal active iodo-colloid to the gland. 8. The removal of sufficient secreting tissue relieves the symptoms of the disease.

The bearing of these facts on the various theories which have been put forward to explain Graves' disease, 'toxic' goitre, and endemic goitre must be discussed. Each theory is based upon the supposition that secretion proper and iodo-colloid are mutually derivative substances.

According to the oldest theory secretion proper was the mother substance of iodo-colloid. If secretion were the mother substance from which iodo-colloid is derived, then the greater the active accumulation of iodo-colloid the greater should be the evidence of secretory activity. This does not occur, for in Graves' disease there may be no iodo-colloid, yet secretory activity is at its maximum. Also in colloid goitre (struma colloides diffusa), where there is the maximum influx of iodo-colloid, there is no secretory activity. For these reasons Marine, who first demonstrated the effect of iodine on the thyroid physiology, was driven to formulate a second theory, namely, that secretory activity depended upon an excessive demand for circulating iodine. The secretory activity arising under these circumstances should be evident in the well-filled iodo-colloid follicles. This does not occur. Where the secretory follicles are well filled they are filled with secretion, and not colloid. The secretion itself contains no iodine, while secretory tissue (i.e. cells) holds but a minimum of iodine, and this modicum is inactive iodine. Nor, were Marine's theory valid, could the demand be satisfied by diminishing the supply as is done by operation in Graves' disease. Nor could excessive secretory activity be induced by increasing the supply of iodine in the body as occurs in 'iodine Basedowii' (Williamson and Pearse (25)). Furthermore, it has been shown that iodo-colloid can be stored at the same time as secretory activity is maintained. These and other contradictions led to the

formulation of a new theory. A dystrophy of the iodo-colloid function of the thyroid in Graves' disease is now postulated. The secretion contained in the secretory areas is said to be a thyroxin-poor colloid. In this theory, also, there is recognition of the fact that the secretion is *not the mother substance* of iodo-colloid. The revised theory would seem to imply that the secretion is the residue after the iodo-colloid has been depleted of its iodine molecule. In this way, according to theory, iodo-colloid becomes the mother substance of secretion. *It will be obvious that both theories explain 'secretory activity' by presuming a disorganization of the iodo-colloid function of the thyroid tissue in Graves' disease.*

Now when ½ to ⅔ of an adenoid goitre containing no active iodo-colloid was amputated, the remainder of the gland at once stored iodo-colloid. This occurred in spite of the fact that no iodine was administered. From this fact alone we must conclude that the iodo-colloid function of the thyroid is not disorganized in Graves' disease. Obviously iodine, or the precursor of thyroxin, or iodo-colloid, was circulating in the body. The tissue removed at operation had, while in the body, inhibited the deposition of iodine as iodo-colloid *in the gland.* In adenoid goitre presumably the whole iodo-colloid capacity is exercised, while in other cases the reserve is only partially depleted. In some unknown way secreting tissue is apparently responsible for keeping the iodo-colloid mobilized. Clearly, it is the opportunity rather than the capability to elaborate iodo-colloid that is lacking in the gland of Graves' disease.

The same lesson is to be learned from the effect of iodine administration. Iodine feeding re-establishes a reserve of active iodo-colloid in the gland. Therefore there can be no disturbance in the iodo-colloid function of the thyroid tissue. Thus, the main basis of the theories whereby the two substances are regarded as mutually derivative has no grounds in fact.

In Graves' disease the gland is quite capable of elaborating a normal iodo-colloid. Moreover, there is apparently an excess of iodo-colloid in the circulation, as measured by the metabolic rate and by the reappearance of a store of iodo-colloid after simple amputation without iodine feeding.[7] Now if this high demand for iodine is met by excessive secretory activity in the thyroid, then the removal of areas of secreting tissue should not *diminish* but rather *increase* the secretory activity in the residue of the gland. Furthermore the secreting tissue cannot be a residue from the digestion of stored iodo-colloid, since we have seen that where secretory activity is most apparent, i.e. in adenoid goitre, there is no iodo-colloid to be digested. Nor does the 'secretory residuum' contain iodine, even when iodine has been freely fed. There is therefore no evidence that iodo-colloid is the mother substance of secretion.

But even if it were possible to grant this contention it would only emphasize the importance of 'secretion proper'. Secretion proper would remain an entity

[7] Figures for iodine values of the blood in Graves' disease demonstrate the same possibility (Breitner (5), de Quervain (18)).

as well as a necessity of normal thyroid function. It would have to be absorbed or utilized and would retain its faculty for being toxic as in Graves' disease.

The facts lead to the inevitable conclusion that there is no disturbance of the iodo-colloid function of the thyroid gland in Graves' disease. It is clear, therefore, that the secretory activity is caused neither by a hyper-activity of the iodo-colloid function nor by a dystrophy of the iodo-colloid function. It is out of these two assumptions that arises the confusion of the two distinct and very typical physiological activities of the gland.

We must therefore add the therapeutic evidence adduced in this study to the physiological, anatomical, and pathological evidence previously brought forward in support of duality of function in the thyroid gland. The facts justify the description of two separate functions: 1. The secreting function; 2. The iodo-colloid function.

The relation of the two functions to the clinical syndrome. When secreting tissue is amputated, not only is the excess of circulating iodo-colloid returned to the gland, but the symptoms of intoxication disappear. The removal of a very small amount of secreting tissue can abolish the intoxication. Thus, the secreting tissue is directly responsible for the intoxication.

We should therefore speak of the intoxication of Graves' disease as associated with a disturbance of the secretory function of the thyroid gland. The only other knowledge at present available is that this disturbance is not a quantitative one. But there is evidence that there is for each case a *critical* amount [8] of secretory activity which feeding with iodine cannot displace. This critical amount may occupy the whole goitre and so prohibit iodo-colloid storage, as in two instances in this series (see also Halsted (10); Williamson and Pearse (25)).

In an earlier study (Williamson and Pearse (24)) it was indicated that if these two functions of the thyroid were recognized as entities, then two symptom-complexes would probably be found in the syndrome of Graves' disease. Plummer (16) independently and on clinical grounds has arrived at a similar conclusion and has grouped the two series of symptoms. One group he considers due to an excess of circulating thyroxin, and this has been demonstrated; the other due to what he calls 'poor substance', which is identical with 'secretion'. The clinical evidence available, therefore, supports the evidence drawn from therapeutics already discussed.

It has been shown that the secretion (or poor substance) is the factor which mobilizes the iodo-colloid to an excessive amount.

One other finding raises the question of the relationship of Graves' disease to iodine metabolism. It is clear that the intoxication in the disease depends neither upon a loss of the thyroid reserve of iodo-colloid nor upon an excessive reserve of iodo-colloid. Iodo-colloid *in the gland* is not in itself responsible for the intoxication.

This being so, it is evident that in the course of Graves' disease the loss of a reserve of iodo-colloid, as in adenoid goitre, may imply a lack of necessary

[8] This is also true of normal thyroid (Halsted).

circulating iodine. There could not have been an *absolute* deficiency of iodine, since a reserve appeared in the gland after simple partial amputation. But iodine feeding had the same effect—it re-established a reserve—so that there may have been a *relative* lack of iodine in the circulation in 48 per cent. of cases, viz. those with adenoid goitre. This relative deficiency cannot account for the symptoms, since 52 per cent. of the goitres, in the non-iodized group, already contained an abundant reserve of iodo-colloid. Further, in the other group of cases, any relative lack of iodine had been repaired by feeding. This relative lack of iodine is not, in itself, responsible for the intoxication which necessitates surgical treatment. It may nevertheless contribute some feature to the symptom-complex. If this is so, then the clinician should be able to discern the quantity or quality of that part of the intoxication due to the relative shortage of iodine. Until this is done the value of iodine as a therapeutic measure in Graves' disease and its limitation will remain undetermined.

Conclusions.

This study of the effect of therapeutic measures in Graves' disease provides further evidence of two functions in the thyroid physiology. These are: (*a*) The secreting function; (*b*) The iodo-colloid function.

These functions are not mutually derivative, for it has been shown that iodo-colloid cannot be the mother substance of secretion proper, nor secretion proper the mother substance of iodo-colloid.

The relation of the two functions to Graves' disease is shown by the following findings:

1. The secretory activity of the gland is directly related to the thyrotoxicosis of Graves' disease.

2. The thyrotoxicosis is relieved by simple removal of pure secreting tissue.

3. Iodo-colloid function has only an indirect relation to the thyrotoxicosis.

4. An absolute loss of a thyroid *reserve* of iodo-colloid can occur in Graves' disease (48 per cent. of cases).

5. This mobilization of colloid depends upon some factor in the secretion, for the following reason: When iodine feeding is excluded, excision of pure secreting tissue causes, or allows, a reserve of active normal iodo-colloid to reappear in the remainder of the gland.

6. Iodine feeding can also re-establish a reserve of normal active iodo-colloid in the gland.

7. However the thyroid reserve of iodo-colloid is re-established it does not abolish the thyrotoxicosis.

8. There is no absolute lack of circulating iodine in Graves' disease, but—

9. A *relative* lack of circulating iodine may complicate Graves' disease (48 per cent. of cases).

10. This relative lack of iodine is relieved by iodine feeding, but the effect on the thyrotoxicosis is not yet clear.

We wish to express our gratitude to Sir James Berry, Professor George Gask, Professor Francis Fraser, and to Mr. T. P. Dunhill for their whole-hearted co-operation and for their material which made the work possible. The research was undertaken for the Medical Research Council.

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DESCRIPTION OF PLATES.

PLATES 1 and 2, FIGS. 1–6. A series of goitres from cases of Graves' disease to show the wide variation in the amount of secretion tissue and colloid tissue respectively.

Fig. 1. Adenoid goitre containing no colloid but a great amount of secretion.

Figs. 2–6 show the effect of iodization. Both colloid and secretion are present in these glands in various amounts.

There is apparently a critical amount of secreting tissue peculiar to each case which iodization cannot affect.

FIG. 7. Tadpoles of the same age: feeding begun on 10th day. a = secretion; b = control; c = thyroxin; d = colloid.

FIG. 8. Tadpoles of the same age: feeding begun on 30th day. a = secretion; b = control; c = thyroxin; d = colloid.



FIG. 1



FIG. 2



FIG. 3



FIG. 4

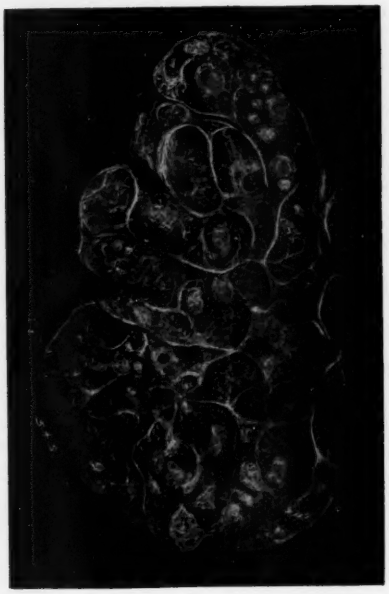


FIG. 5



FIG. 6

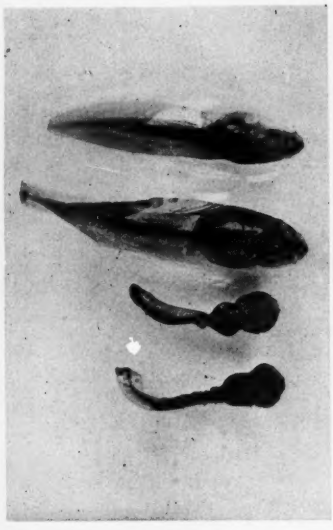


FIG. 7

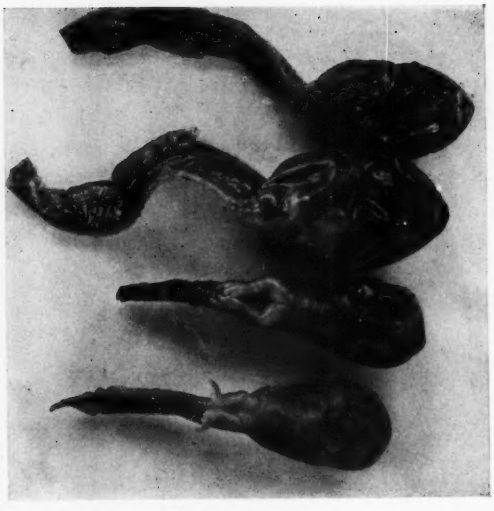


FIG. 8

THE CLINICAL APPLICATION OF TOTAL CHLORIDE ESTIMATIONS IN THE FRACTIONAL TEST-MEAL; WITH AN ANALYSIS OF A SERIES IN FIFTY NORMAL CHILDREN [1]

By W. S. C. COPEMAN and N. GRAY HILL

The fractional test-meal has of late years been subjected to frequent and severe criticism, largely on the grounds that the clinical information to be gained from it is of little more value than that obtained from the Ewald meal, when compared with the labour entailed in the collection and estimation of the requisite specimens, and is, indeed, sometimes actually misleading.

The method has not, so far as we are aware, been applied to the investigation of gastric disorder in childhood to any considerable extent, owing probably to the increased difficulty of collecting the specimens, and to the lack of a normal series for comparison during this period of life. The objects of this investigation were to produce such a series and to compare them with the findings of other observers in adults, and to endeavour to establish the general usefulness of the fractional test-meal by eliminating the grosser misleading factors and a certain number of the usual estimations.

From the purely clinical point of view, all that presumably is essential is a short curve which will show at a glance whether the stomach is reacting, within physiological limits, in response to the normal stimulus of food. For this purpose an actual secretory curve would obviously be desirable, but is not as yet possible of attainment.

The present series of complete fractional test-meals were performed on a group of fifty children between the ages of 8 and 16, who were, so far as is possible, comparable. They were all cases convalescent from rheumatic heart disease or surgical tuberculosis, whose hearts were well compensated, and who were living a healthy open-air life under the best possible conditions. No child had any clinical abnormality of the digestive system, and being of the same social status (L.C.C. schools), their previous dietetic habits may be presumed to have been similar.

Curves of free HCl and Total Acidity.

The curves generally plotted for the fractional test-meal are those of free HCl and of total acidity. The former curve can tell us little more than the fact that acid gastric secretion is being produced, since the factors which influence the pH of the stomach contents are so numerous and so controversial, that further

[1] Received July 4, 1928.

deductions of importance are scarcely legitimate, unless arrived at with the aid of other estimations. The latter curve, in most cases, runs at a slightly higher level, but parallel with the curve of free HCl, and is only of interest in cases in which the latter curve is non-existent or very low.

It is probably true that the HCl curve is an indication of the continual process of gastric secretion and neutralization due to pyloric regurgitation, since the shape of the curve must depend on three factors: (*a*) the amount of juice secreted, (*b*) the amount of neutralization taking place in the stomach, and (*c*) the rate at which the stomach empties.

A further argument against the routine employment of the curves of free HCl is their extraordinary variability both at different times in the same subject, and even during the course of the same meal. As we and others have been able to show, these variations depend on local rather than general causes. Butcher (1), by withdrawing a stomach tube during the course of a test-meal, noted a coincident difference of 10 points of acidity between the fundal and the pyloric ends of the stomach. They can be produced deliberately, and shaking the patient or kneading the gastric area at intervals during the meal would probably safeguard against this. Time of titrating also varies the results appreciably.

The curves of acidity may, when employed, be classified either according to their shape or else according to the height to which they rise.

With regard to their shape, Bennett and Ryle (2) found that 90 per cent. of their normal adult series showed a definite peak, whilst of the remainder half showed an achlorhydria and half a curve of the 'climbing' type (as in pyloric ulceration). These findings were not entirely confirmed in the present series, the figures being as follows:

Curves with definite peak . . .	38 %.
Of 'climbing' type.	20 „
Of 'plateau' type	32 „
Of achlorhydric type	10 „

With regard to the curves of the 'climbing' type, the diagnosis of hypersecretion of acid was in none of these cases found to be justified on consideration of the curve of inorganic chloride which was estimated coincidently, the evidence being merely that of defective neutralization and not of abnormal secretion. Further, of the high percentage of cases of achlorhydria, none of these cases can, on any grounds other than consideration of the HCl curve alone, be considered to have been true examples of this condition, in view of the fact that the chloride curves were found in each case to be normal or high. This type of case occurred in Bolton and Goodhart's series (3), and is quoted by them in evidence of the assertion that 'achylia gastrica' cannot, by means of the ordinary HCl curve, be differentiated from cases of early and persistent neutralization of a normal gastric juice. In the light of our experience we are inclined to doubt the presence of true achlorhydria in health.

With regard to the classification of the acid curves according to the height to which they rise, Bell has proposed the following modification of Bennett and Ryle's original division of their normal series of 100 students (4):

Group A. Achlorhydria; no free HCl present at any time in the gastric juice.

Group B. Hypochlorhydria; at no time is there more than 10 units of HCl present.

Group C. Normal; (1) high, (2) low; never more than 60 units present.

Group D. Hyperchlorhydria; at some time more than 60 units present.

A unit of HCl is defined as the equivalent of 1 c.c. of N/10 HCl per 100 c.c. gastric contents.

The comparison by these means between Bennett and Ryle's series (2) and our own is shown in Table I:

TABLE I.

Group.	Bennett and Ryle.	Present Series.
Group A	4 %	10 %
Group B	1 %	10 %
Group C	87 %	68 %
Group D	8 %	12 %

It will be noticed that although the tendency is for the majority of cases to fall into Bennett and Ryle's 'normal' category, the cases in the present series are more evenly distributed over the other categories. The value of these groupings will be further referred to in connexion with the total chloride findings.

Emptying-time of Stomach.

In the present series, as judged by the disappearance of starch, this was on the whole considerably in excess of that usually considered normal, particularly when it is remembered that the stomach of the child is generally supposed to possess a greater degree of mobility than that of the adult.

The cases were grouped into their categories for purposes of comparison with the figures given by Bennett and Ryle in their paper on the subject (2): (i) achlorhydria, (ii) normal, (iii) 'climbing' HCl curves. The presence of bile was in our series extremely inconstant, and could not definitely be correlated with the shape of the chloride curves.

TABLE II.

	Bennett and Ryle.			Present Series.		
	No.	Mean Max. HCl.	Mean Emptying Rate.	No.	Mean Max. HCl.	Mean Emptying Rate.
i. Normal	91	33	1·9 hrs.	35	40	2·17 hrs.
				5	0	?extremely rapid
ii. Achlorhydria	4	0	1·1 „			
iii Climbing	5	70	2·2 „	10	75	2·33 „

TABLE III. *To show Variations in Emptying-time of Stomach between our Series and* 100 *Normal Adults* (Bennett and Ryle).

Time.	½ hr. or under.	¾ hr.	1 hr.	1¼ hrs.	1½ hrs.	1¾ hrs.	2 hrs.	2¼ hrs.	2½ hrs. or over.	Mean.
Bennett and Ryle	1	5	3	7	13	17	14	18	22	1·9 hrs.
Present series	4	1	0	0	0	3	4	5	22	2·16 hrs.

It was noticeable that in the 'achlorhydric' group starch was consistently absent at all periods. This is difficult to explain. The food may (*a*) have passed straight through the stomach into the small intestine, or (*b*) have become hydrolysed with abnormal rapidity by the ptyalin of the saliva. With the object of testing the latter possibility, small amounts of the meal were incubated at 37° for periods varying up to 180 minutes with the saliva of these patients, and with the saliva of a normal adult (N. G. H.) as control. It was found that in the absence of hydrochloric acid it was possible for starch to disappear after 30 minutes, provided that the quantity of saliva was sufficient, although monosaccharides could still be demonstrated. This (*b*) therefore seems to be the most likely explanation. We are investigating this point further.

Bennett and Ryle mention that they have found achlorhydrias whose stomachs were empty in half an hour, although they state that some will delay up to 3·25 hours, the average being about 1·6 hours, a little less than the normal average. Bell (4) selected 51 cases of achlorhydria, and found the average to be only a quarter of an hour less than for the normal subject.

In the 'normal' group the chief point of interest lies in the fact that so many of the stomachs still contained starch at the end of 180 minutes.

In the 'climbing' group of hyperchlorhydriacs are a large number of the total series; this is interesting in view of the statement of Smith and Miller (6) that youthful subjects show abnormal acidity less frequently than do older ones. In this group the average emptying rate was 2 hours and 20 minutes.

Willox (5), estimating the gastric mobility in children by means of the barium meal and X-rays, concluded that the stomachs of older children empty quite as quickly as those of younger children, if the bulk is equal, the average being 3·4 hours, although in some cases the food begins to pass through the pylorus practically as soon as the meal has been taken.

Inorganic Chlorides and Total Chlorides.

If the curve for free HCl be read in conjunction with the curve of inorganic chloride formation, it has been seen that information of some value can be procured, since these curves are, in the words of Bolton and Goodhart, a 'balance between two processes—secretion and neutralization'. It is therefore essential, if possible, to find some common factor which will approximately express the true state of the gastric response, since neither can represent in any way a secretory curve. This, it is suggested, may be found in the estimation of the total chlorides.

The stomach juice may be said to contain hydrochloric acid in three forms at any moment during digestion: free HCl; protein HCl (the two together constituting 'active' HCl); and neutralized HCl, this latter constituent being represented by the inorganic chlorides. The common factor of these curves can be represented by the estimation of the total chlorides. This curve must, therefore, approximate fairly closely to a secretory curve, and of all the curves is the one which is found to maintain the most constant shape over a large series of meals. It is stated by Ryle that this curve rises when the stomach secretes, and falls when the contents of the stomach are diluted by the addition of a fluid containing a less proportion of chlorides than there was previously present; this curve may fall to a level of 0·2 per cent. chlorides, which, as Goodhart has pointed out, is the normal chloride content of pancreatic juice.

It would seem, therefore, that, for purely clinical purposes, it would be more reasonable to substitute for the usual curves that of the total chlorides, although comparatively little attention has been paid to it in the past; probably, as suggested by Patterson (7), owing to the technical difficulties involved in this estimation. He has, however, put forward a simple modification of the usual Volhard method which would appear to be adequate in those cases where this difficulty arose. The adoption of this curve would moreover eliminate two sources of possible error which may arise when the HCl curve is being used, namely, excessive salivation and duodenal regurgitation due to retching during the passage of the tube.

Consideration of the Total Chloride Curve.

As would be expected, the shape of the total chloride curve differs from that of the other curves, marked peaks, for instance, being unusual. In our series the majority were of the 'climbing' type, peaks, if occurring at all, doing so towards the end of the chart when duodenal regurgitation might be expected, although bile did not by any means always appear in the specimens at this point; whilst, conversely, bile on several occasions was present without any peak occurring in the total chloride curves. The presence of bile could not be shown to determine whether the curve was to be of the 'climbing' or 'plateau' type. The fact that bile was often absent is, according to Boldyreff (8), not an indication that regurgitation had not occurred, since he was able to show that pancreatic juice alone might enter the stomach and cause neutralization, whilst Spencer, Myer, Rehfus, and Hawke (9) showed that trypsin could be found in the stomach in the absence of bile, and that the amount was inversely proportional to the gastric acidity. Possibly secretion of chloride might explain it also.

As would be expected when the acid curve shows no peak, the chloride curve rises continuously, but when the acid curve falls the chloride curve remains level, or continues to rise, never falling much in any circumstances until the stomach empties.

A few curves were of the 'plateau' type.

No physical feature could be associated with any particular type of curve, although such points as appetite, regularity of the bowels, build, colouring, intelligence, &c., were considered in all cases.

A casual glance at the total chloride curves in any series will show that this curve is much less liable to sudden and apparently inconsequent rises and falls than are the free HCl and inorganic chloride curves, and is therefore a suitable type of curve for purposes of simplification. With regard to the normal limits for the total chlorides, comparatively few data are available; the area covered by 80 per cent. of Baird, Campbell, and Hern's (10) series of 26 normal students is shown in Fig. 1, together with our own findings, in 90 per cent. of cases at 60, 120, and 180 minutes. The limits are therefore seen to be wide, but are not much wider than those usually given for the free HCl curve, which is included for purposes of comparison.

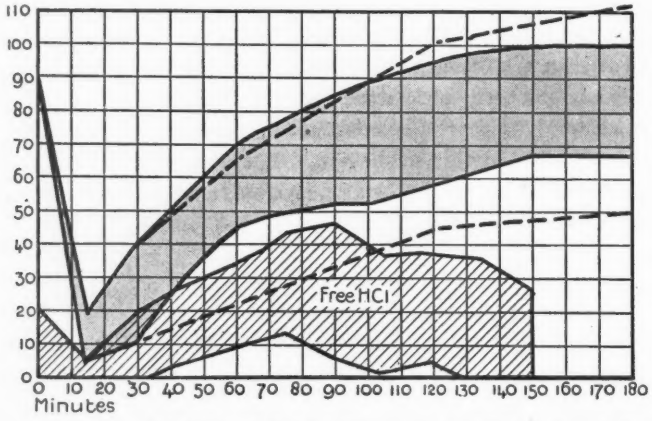


FIG. 1. Shows area (shaded) included by 80 per cent. of Baird, Campbell, and Hern's series (10) of total chloride estimations on 26 normal students. Dotted line indicates limits for 90 per cent. of present series of 50 normal children. Normal (Bennett and Ryle) HCl curve included for comparison.

If the chloride estimation is, as suggested above, to be the one taken for clinical use, it must be considered how it is to be presented. In Germany a fraction is occasionally worked out which is known as the 'chloride index', that is, the percentage of the chloride expressed as HCl:

$$\frac{\text{total acidity}}{\text{total chlorides}} \times 100 = 40.$$

To use this unit, however, seems an unnecessary and rather unduly arbitrary procedure, involving also the estimation of the total acidity, and it is proposed that certain actual points on the total chloride curve, in grammes per cent. of HCl, be employed, as shown in Fig. 1.

The total chloride curve shows in most cases a sudden fall after the digestion of the meal, which is comparable with that seen in the free HCl curve. This is of no clinical significance, and practically constant, and can therefore be omitted for purposes of simplicity.

The main tendency of any simple curve can be shown in its crudest form by three plotted points. It remains, therefore, to decide if such a curve would be sufficiently accurate for our needs, and if so, which are the most suitable points to be taken.

At 60 minutes—a convenient time period practically—the curve is generally found to be commencing on the upward grade again after its initial fall. This point is the first one to be plotted.

All the curves in this series, with one exception (? experimental error), continued from this point to rise to an apex about 120 minutes after the ingestion of the meal. This was therefore taken as the second point on the curves. Subsequently it was noticed that the curves might be of one or two types:

(*a*) those which continue to rise after 120 minutes (majority),

(*b*) those which fall after this point.

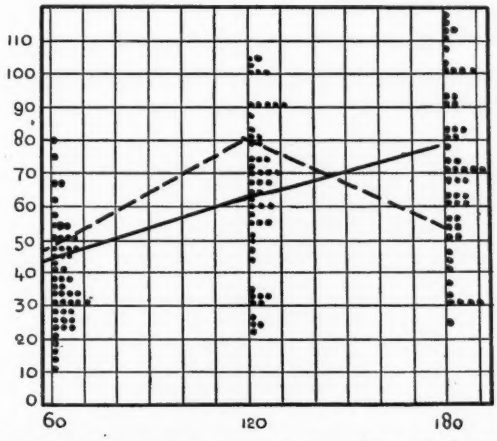


FIG. 2. Showing the total chloride readings at their time periods, with mean curve of both rising and falling types in series of 50 normal children.

Since, however, if the average of each of these two types of curve be plotted and compared with the total area covered by the complete series of total chloride estimations (Fig. 2), it will be seen that both types fall well within the area covered by 90 per cent. of the complete series (Fig. 1), they may be ignored in practice.

The third and last point plotted on the curves was the usual 180 minutes.

Superficially these points when plotted appear to express adequately the general shape of the total chloride curve from which they are isolated, the normal limits of variation in 90 per cent. of cases at these three points being shown in Fig. 3.

It has been mentioned above that the free HCl and inorganic chloride curves, if read in conjunction, will express a balance between the two processes of secretion and neutralization which must at any moment be taking place in the gastric contents.

If we now take the mean figure for these two curves at the three periods suggested above, and in every case plot the result with that expressing the total chloride content, it will be found that the shape of the two curves will in every case be very similar, the latter curve being, however, an exaggerated version of the former (Fig. 4). It would appear, therefore, that the inclusion of these two

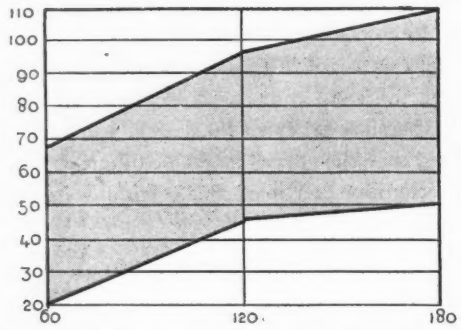


FIG. 3. (Shaded area includes 90 per cent. of total chloride estimations in present series, and is suggested as a standard for comparison with future series.)

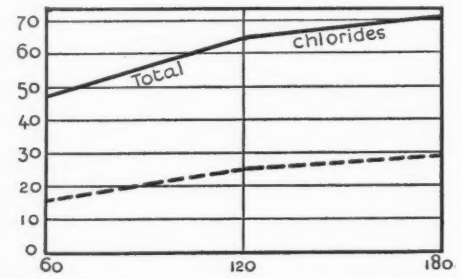


FIG. 4. Comparison of mean curves of total chloride (dark line) with curve expressing mean of all free HCl and inorganic chloride estimations for same series of 50 cases, showing similarity in shape.

curves is unnecessary if the total chloride curve be adopted, although it would be reasonable to estimate roughly the free HCl in the last specimen in order to be in a position to state whether true hyperchlorhydria were present or not, if it were suspected.

The actual chloride content of the meal need not be considered as a possible source of error, since this will remain approximately constant in all cases, and may be considered as the lowest point on the curve.

Summary.

A group of 50 apparently healthy children between the ages of 8 and 10 were subjected to the fractional test-meal, and the results analysed and compared with the findings of various observers in adult subjects. They were found to vary in certain respects.

It is considered that the usual estimations for free HCl and total acidity are not of much clinical value, owing to their variability, even in the same individual, at short intervals.

It is suggested that it is desirable for the clinician to be provided with a short curve, which is less liable to experimental error, and which will show at a glance whether the stomach secretion is reacting within normal limits to the stimulus of food.

It is suggested that such a curve, in the absence of a true secretory curve, may be provided by the estimation of the total chlorides. The limits within which the total chlorides of 90 per cent. of our normal cases varied are plotted and shown in Fig. 1. These limits are not much wider than those generally accepted for free HCl, and it is suggested that such curves would yield more accurate information. It is proposed to simplify the procedure by plotting only three points. A chart based on this is given in Fig. 3 for purposes of comparison with future series.

An investigation into the emptying rate of the stomach in these children, as evinced by the disappearance of starch, seems to cast doubt on the common idea that the emptying rate of the child's stomach is more rapid than that of the adult.

The current theory that the stomachs of 'achlorhydriacs' apparently empty at a faster rate than those of normals is, however, borne out, although evidence is produced to show that in these cases the ptyalin of the saliva is much more active; the disappearance of starch is, therefore, probably not unrelated to this fact in most cases.

We wish, in conclusion, to thank the following who have helped us: Dr. T. Gordon Pugh, for facilities for the work to be carried out at Queen Mary's Hospital, Carshalton; Professor F. Langmead and Dr. H. E. Archer, for suggestions and advice; and Miss Liddiard, for technical assistance in the estimations.

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DYSPHAGIA AND ANAEMIA[1]

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Dysphagia is not generally recognized as a sign of anaemia; in no text-book of medicine is it described, and a careful search through the records of the Victoria Infirmary, Glasgow, reveals no mention of it in pernicious anaemia or the leukaemias. Even from the hysterical manifestations of chlorosis it is omitted, for although reference is frequently made to globus hystericus, and van Noorden (1) notes ten examples of anaesthesia of the pharynx in a summary of 255 cases of chlorosis, the former is not usually, and the latter is not necessarily, accompanied by any difficulty in swallowing. The description by Plummer in 1914, Vinson (2) in 1922, Moersch and Milton Conner in 1926 (3), and by Brown Kelly (4) and Paterson (5) in this country in 1919 of a syndrome in which dysphagia was associated with a form of anaemia, at times indistinguishable from splenic anaemia, was therefore of interest and value, and it is rather surprising that more attention was not paid to it until quite recently, especially as the condition is far from uncommon in general practice. The American authors in their accounts are obviously more impressed by the debility and anaemia than by the pharyngo-oesophageal condition; the British laryngologists lay stress on the local changes in the mouth and pharynx and attribute the dysphagia to spasmodic contraction at the oesophageal entrance; Plummer described it as hysterical dysphagia.

Sex and age incidence. Most of the recorded cases have occurred in middle-aged women. In Moersch and Conner's series of 65 cases all were women, 59 of whom were married. The youngest patient was 23, the oldest 63; the average age was 45.

In Vinson's 69 cases 57 were women, in the present series (Table I) all were women; the average age was 48·5.

Social and personal condition. It is difficult to estimate what class of the community, if any, is the more affected; no statement is made on this point in the Mayo Clinic examinations; some of the patients in the present series were poor, under-nourished women, most of them were private patients of good social standing.

Syphilis and alcohol as causative factors can be excluded, and though many sufferers are nervous, easily worried, and upset, some of them state that their nervousness is due to their fear of choking, and only commenced with the onset of dysphagia.

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Symptoms. The dysphagia is referred to the level of the larynx, and the complaint is made that there is an unusual tightness of the throat or that something behind the larynx is gripping the food. Often this symptom is more exaggerated when the woman is tired, and is more troublesome at an evening meal than at breakfast. Sometimes there is a story of having been choked by a particular piece of meat or bread or vegetable, or of a piece of crust or a raisin having 'stuck in the throat'. It is uncommon to get an account of the throat having been scalded by hot food or fluid, though sometimes dysphagia is dated from the impaction of a sharp substance such as fishbone. In the only case I have seen in a man, it followed the hasty swallowing of a cocktail in which a rather large piece of lime peel was floating which 'caught' at the back of his throat. At other times the onset of the dysphagia is gradual, and sudden attacks are separated by long intervals in which deglutition proceeds normally. The result, in the long run, is the same, and food has to be masticated and swallowed with punctilious care; inevitably the diet becomes reduced—meat, vegetables, fruit are banned, bread unless softened is feared, and tea or coffee and semi-solids become the daily fare. Even then there may be frequent catching of a fragment at the oesophageal entrance and distressing attempts are made to dislodge it, while regurgitation takes place if water is used to wash it down. The eating of meals amongst strangers becomes a nightmare and conversation, or indeed any distraction from the immediate task of swallowing, is impossible.

In the milder and earlier cases, examination of the mouth and pharynx may reveal nothing beyond a pale and waxy-looking mucous membrane, with the tongue smooth and devoid of papillae. Later there are fissures extending downwards from the junctions of the lips and the pharyngeal mucosa is parchment-like, dry, and atrophic, with a tendency to bleed on manipulation.

Brown Kelly describes the endoscopic appearance in patients who had been affected for years thus: 'It was found that the deepest part of the hypopharynx did not present the usual sphincter-like appearance. Instead of rounded folds or cushions of mucous membrane forming a stellate arrangement, tense bands passed in various directions with their thin edges pressed tightly together. The entrance to the oesophagus appeared as a pinhole or small irregular opening, or obliquely placed slit, and was not always in the middle line. Sometimes one half of the mouth of the gullet seemed closed by a web passing back from the cricoid.' He concludes, from the manner in which the folds fell apart on manipulation, that the stenosis was due to their firm approximation and not to organized adhesions between them. He is therefore of opinion that the affection is caused by a spasm at the entrance to the oesophagus and only exceptionally by a membranous stricture.

Dan MacKenzie (6) has reported two similar and pronounced cases of post cricoid spasmodic stricture. He found, in both, the lumen reduced to a small circular orifice of 3–5 mm. The stricture resisted dilatation with the tube, but yielded easily to a bougie.

Vinson, in his paper, while agreeing that the mucosa of the mouth and

pharynx is often dry and atrophic, states that no oesophageal web was ever seen by him, and in this Moersch and Conner concur, although the latter authors come nearer to Brown Kelly's opinion when they remark that, 'While none of our patients complained of a lump in the throat, they said that during the periods when they were able to eat they could feel something relax in the throat. Might it not be possible that, due to some nervous strain, such a spasm occurs or is even brought on through an infection? In the final analysis, the condition may be found to be on the same basis as cardiospasm.' These authors, as I have already indicated, deal more fully with the blood condition, and before turning to this aspect of the syndrome, it only remains to be said that many of the cases under consideration also have cardiospasm. Whether this is due to reflex spasm consequent on the condition at the upper end of the oesophagus, or is the result of similar atrophic changes in the mucous membrane of the epicardiac canal, is unknown, but as it is advised not to pass the bougie into the stomach and only past the upper constriction when cardiospasm is also present, one would imagine that a reflex spasm is the more logical view.

Blood changes. The pallor is very noticeable and suggests the facial appearance of pernicious or a severe secondary anaemia; no degree of jaundice has yet been described. The detailed blood examination of 18 cases is given in the table on p. 49, and an estimation of the hydrogen-ion concentration of the saliva is to be found in one column. In general the changes in the blood are those of chlorosis or mild secondary anaemia, with a constant and considerable reduction in the percentage of haemoglobin. Here the average is 51·8 per cent., in Moersch and Conner's statistics 48 per cent. The average red corpuscle count is almost exactly 4 millions; Moersch and Conner give 3,890,000 per cm. There is no change in the leucocyte count and the differential examination calls for no comment, except in Case 2 in the table, where the grade of anaemia was not only more like pernicious, but in which numerous nucleated red corpuscles and a high percentage of myelocytes were found. This case was in many ways similar to one recently reported by Mason Jones and Owen (7).

Associated with the alterations in the blood there may be enlargement of the spleen; according to the Mayo Clinic findings it may fill one quarter of the abdomen. In this series 27 per cent. showed quite definite enlargement, and this is probably a conservative estimate. In Vinson's 69 cases, 12 had splenomegaly; of Moersch and Conner's 65, 20 were enlarged.

The signs of this syndrome may therefore be briefly summarized—glossitis and atrophy of the oral and pharyngeal mucosae, definite reduction in haemoglobin percentage, and some diminution of red blood corpuscles, frequent enlargement of the spleen, and the symptoms—dysphagia referred to the level of the larynx, with loss of appetite, debility, and nervousness.

Differential diagnosis. The differential diagnosis must embrace all forms of dysphagia at the upper end of the gullet, and after excluding the central lesions which result in bulbar paralysis, the following commoner conditions in this area must be considered: ulceration from tuberculous, syphilitic, or malignant disease;

a stricture following injury or the ingestion of a corrosive poison; cardiospasm referred high up in the gullet; diverticula; aneurysm, or mediastinal tumour pressing on the oesophagus or congenital webs of the oesophagus.

The diagnosis is made on the negative results of X-ray, Wassermann, and neurological examinations, the absence of clinical evidence of malignant disease, aneurysm, or other obstruction to the onflowing oesophageal contents, and the absence of any history of swallowing corrosive or other destructive liquid, while on the positive side there is an anaemia without any substantial loss of weight, a reduction of haemoglobin, frequent enlargement of the spleen, and the fact that the dysphagia is often as marked on the first day of the disease as on the last; finally, the preponderance of these cases amongst women of middle life will naturally be considered.

Treatment and results. The treatment is fortunately simple and effective, and consists in passing a bougie, oesophagoscope, or some other form of dilator, according to the degree of resistance met with on examination. The Rochester physicians assert that their treatment is entirely suggestive, and that no 'stretching' of the oesophagus is employed; that the passage of *any* bougie is often sufficient provided that the patient is reassured that there will be no more difficulty in swallowing. Cases indeed have been recorded in which a bougie has been passed without improving the condition, and yet at a subsequent visit a smaller bougie has put the patient at her ease and at once. An iron and arsenic mixture or iron alone is ordered, and in successful cases as soon as the dysphagia disappears the haemoglobin percentage rises and the spleen returns to normal size. Plummer in his first account advised the administration of thyroid extract for some time after the dysphagia ceased, on the ground that the prolonged starvation had resulted in a limitation of the body's need for thyroid, and that a disuse atrophy of the gland had set in.

Even the more serious and long-standing cases described by Brown Kelly are usually as easily relieved: 'At the first attempt to swallow after treatment, the patients felt as if something had been removed, and at once announced that they were cured. Two or three days later, when the soreness due to examination had passed off, they ate meat, ham, prunes, and other foods of which for years they had been unable to partake. They also found that they could converse at meals and that they need not pay constant attention to mastication or be nervous about swallowing.

'Some of the patients have had no return of their symptoms after an interval of one or two years; others after a few months have felt the need of care and have shown a slight tendency to choke. In exceptional cases, after a period of improvement lasting from one to three months there has been relapse, but normal deglutition has been re-established—at least temporarily—by passing a bougie.'

Commentary.

In any attempt to elucidate the pathology of this condition, we are faced at the outset by the difficulty of determining whether the dysphagia precedes, or is

the result of, the anaemia. As I have already said, some patients complain of pallor long before dysphagia sets in. In these we may presume that the atrophic mucosal changes at the entry of the alimentary canal are analogous to the glossitis of pernicious anaemia (indeed in twelve of Moersch and Conner's cases the glossitis was that of pernicious anaemia) and are directly responsible for dysphagia. More often, I think, the dysphagia is the first sign, and the dramatic results of treatment suggest that the anaemia is the result of the difficulties of deglutition with the consequent curtailment of foods rich in iron and other essentials.

Hurst (8) thinks that perhaps a streptococcus in the throat is responsible alike for the anaemia and dysphagia. Streptococci can often be isolated in this affection (as can pneumococci, and both are frequently found in any series of throats), but in the few cases I have examined for streptococci I have never yet been successful in agglutinating them with the patient's serum, and the effects of treatment would appear to negative Hurst's suggestion. All other observers are agreed that the condition is the result of a deficient dietary. We cannot, however, neglect consideration of the age of the patients and of the probability of a vicious circle—a debility and anaemia associated with the climacteric, consequent changes in the pharyngeal mucosa, then dysphagia and limitation of food, with resulting accentuation of anaemia and splenomegaly.

The dysphagia is most likely due to inflammation of the nerve endings in the epithelium of the pharynx, the starting mechanism of the reflex arc is at fault, and the swallowing movements suffer; the mucous glands which normally facilitate swallowing in this region are dry and may be atrophic; in short, the swallowing reflex is not normally and instantly initiated and completed. The block takes place at the cricopharyngeus muscle, the lower half of the inferior constrictor of the pharynx, so that technically it is pharyngeal. The nerve supply of this muscle is from the pharyngeal plexus, and also from the external laryngeal and recurrent branches of the vagus; the pharyngeal plexus is formed by branches of the vagus, glossopharyngeal, and the ascending pharyngeal branch from the superior cervical ganglion, and how far this sympathetic supply may bear upon the form of dysphagia under discussion offers a field for conjecture.

In anxiety states, and even ordinarily under the influence of fear, passion, or other emotion, the difficulty of swallowing food is common knowledge and experience, and strongly suggests a sympathetic interference with this muscle.

I know of no exact experimental evidence on this point, and indeed doubt if it could be satisfactorily produced from animal experiments. Wilhelmina Abel (Mrs. Shaw Dunn) and Hofer and Spiegel have shown that in both rabbits and cats no demonstrable change in swallowing was produced in spite of the bilateral removal of the superior cervical ganglion and of the cervical sympathetic belonging to it, or of the stellate ganglion and splanchnic nerves. Very different results followed interference with the vagus, and the changes which were then produced were independent of whether the sympathetic innervation had or had not been retained. These observations, however, were confined to movements

within the oesophagus and were especially directed to movements at the cardiac orifice.

It is obvious that the actual destruction of mucous membrane at the entrance to the oesophagus by an ulcer, fissure, or the impaction of a foreign body may disturb the reflex arc in a similar manner, and in some instances dysphagia is so caused. These lesions in their effects are comparable to the affections of the cardia, which result in the interruption of peristalsis and the stasis of food in the oesophagus; but it must be noted at the upper end of the oesophagus, and for two or three centimetres down, Auerbach's nerve plexus is not interposed between the muscular layers. Such disturbances of function as I have shown before (9) are often the result of inflammatory changes in and around Auerbach's plexus, and are usually the result of an outward spread of inflammatory cells from the mucosa to the intermuscular zone in which the nerve ganglia lie. Any interruption of conduction between the nerve endings on the epithelium and the ganglionic cells, from a simple inflammation to an acute ulcer, might produce similar effects before the ganglia showed any histological change.

The further question of whether we are dealing with a primary spasmodic affection of the cricopharyngeus or whether this muscle, which is normally closed and only opens during deglutition, is in a state of non-relaxation, need hardly be discussed. Our knowledge of neuro-muscular co-ordination, especially in the alimentary canal, is much too limited for dogmatic statements in any direction. My personal opinion, from the survey of the available clinical findings, is that it is likely that both conditions may be found. In the analogous cardiospasm I am convinced that this is so from pathological findings, as I cannot imagine that a layer of inflammatory cells surrounding a ganglion, the cells of which appear microscopically healthy, will necessarily produce the same effect as a lesion in which the nerve cells are destroyed or replaced by fibrous tissue. Both these conditions I have described in cardiospasm or achalasia of the cardia.

The issue is, however, without any real bearing on the causation of this syndrome and with none at all on its treatment, and is only mentioned because of the similarity in the physiological sphincters concerned and their liability to similar pathological effects.

In conclusion, I must refer to the well-known incidence of malignant disease in women of this age and at this site. From 70 to 80 per cent. of all cases of cancer of the hypopharynx are found in women, and it seems improbable that two conditions so related in sex incidence and locale are unconnected. There is no known difference in the histological appearance of the pharyngeal mucosa in the two sexes and no greater liability to damage in women. So that if any connexion exists, it is probably intimate, and it may be that with the climacteric there is at times a proneness to changes in the pharyngeal mucosa which in one results in a dysphagia, and in another, and in greater severity, to malignant proliferation.

My thanks are due to Dr. Porter Vinson of the Mayo Clinic, and to my

colleagues Drs. Glen, Anderson, and Marjorie Gillespie; especially am I indebted to Dr. Brown Kelly, who first drew my attention to this syndrome and placed at my disposal his records and patients.

TABLE.

	Age.	R.B. Corpuscles.	White.	Hb.	Differential.	Saliva pH.	Spleen.
1	45	4,200,000	7,200	50	Normal	6·4	Normal
2	60	3,500,000	5,800	40	Leucopenia	6·2	Enlarged
3	50	3,800,000	6,600	50	Normal	6·6	Normal
4	55	5,000,000	7,200	60	,,	6·9	,,
5	45	3,850,000	6,400	50	,,	6·4	,,
6	47	4,000,000	6,200	55	,,	6·6	,,
7	50	3,820,000	6,100	55	,,	6·6	,,
8	52	4,160,000	6,400	58	,,	n.e.	,,
9	45	3,840,000	6,800	60	,,	6·4	,,
10	50	4,200,000	7,000	55	,,	6·6	,,
11	46	4,400,000	6,800	52	,,	6·6	,,
12	48	3,600,000	5,800	48	,,	6·4	Enlarged
13	47	4,400,000	6,200	50	,,	6·6	Normal
14	46	3,920,000	6,800	48	,,	6·6	,,
15	48	3,300,000	6,700	48	Leucopenia	n.e.	Enlarged
16	44	4,100,000	8,200	50	Normal	6·9	,,
17	42	5,800,000	7,000	50	,,	n.e.	,,
18	45	3,200,000	5,600	50	,,	6·6	Normal
Average	48·5	4,050,000 per c.mm.	6,600	51·8 %			

n.e. = not examined.

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PARKINSONIAN RIGIDITY

A CLINICAL AND INSTRUMENTAL STUDY OF THE EFFECT OF STRAMONIUM, HYOSCINE, AND OTHER ALKALOIDS[1]

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With Plates 3 and 4

Following the epidemics of encephalitis lethargica various residual phenomena have been observed. The most common of these is the Parkinsonian syndrome. This may follow immediately on the acute attack, or develop months or even years after the acute illness has been forgotten. It constitutes one of the most serious problems of the disease, for it may occur as a sequel to even the mildest attack, and once established tends to progress till the patient is reduced to a hopeless state of paralysis and inefficiency.

Many therapeutic agents have been advanced as benefiting the condition. Craig (2) reported some slight improvement in the rigidity and mental state following artificial infection with malaria. McCowan and Cook (16), however, stated very definitely that this form of treatment was dangerous and produced no material improvement. MacBride and Carmichael (17) found that intravenous injections of sodium salicylate improved two out of three cases ; a further trial of this form of therapy has convinced one of us (E. A. C.) that no benefit accrues from its use. Fuller (6) advocated the use of colloidal gold and silver preparations. Visher recorded improvement after intravenous injections of mercurochrome : a trial of this at the National Hospital, Queen Square, made on the suggestion of Dr. Kinnier Wilson, failed to confirm its value. Hyslop (12) found that grain 1/30 of nicotine sulphate relieved rigidity for a few minutes only ; Moll (19), however, using the same drug hypodermically in doses up to grain 1/10 thrice daily, reported considerable improvement in nine out of thirteen cases ; he suggested that the nicotine influenced the prespinal reflex subserving plastic tone. Hall (7) in 1926 thought that the rigidity in his patients was reduced by doses of 30 minims of tincture of belladonna. Szyszka (21) had previously published clinical records of improvement following atropine by the mouth. Hyslop (12), however, failed to find improvement after either grain 1/100 of atropine sulphate or 30 minims of tincture of belladonna. As early as 1906, Erb (5) had recorded the use of hyoscine for the rigidity and tremor in idiopathic paralysis agitans. Babinski and Souques (1), at a discussion on encephalitis lethargica and its sequelae in 1921, mentioned the beneficial effect of hyoscine. Hyslop (12), in a paper reviewing the improvement observed clinically after various therapeutic measures, wrote in 1922 that in six out of eight cases the rigidity was lessened by hyoscine. Kennedy, Davis, and Hyslop (14)

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obtained similar results in a series of cases. Delmas-Marsalet (4) graphically recorded the diminution of rigidity which occurred about forty-five minutes after the injection of hyoscine hydrobromide; this work was confirmed by Cruchet (3). By giving doses of hyoscine hydrobromide up to grain 1/25th, Hohman (10) in 1924 was able to produce improvement in eighteen cases, seven of which were much benefited mentally as well as physically. McCowan, Harris, and Mann (18) came to the conclusion in 1926 that hyoscine was of undoubted value. They were able to demonstrate an improvement in the blood sugar curves of their patients, and this action they assumed to be specific for the drug, though they thought that some of the clinical improvement was due to suggestion; the subcutaneous route was more efficient than by mouth. Ross (20) later argued that the improvement could not be due to suggestion and was probably a direct effect of the hyoscine. After recording the rapidity of movement in a large number of cases, Hall (8) was able to demonstrate in 1927 an increase in the rapidity of movement following hyoscine treatment. Harris (9), by taking tracings of the knee-jerks before and after treatment, concluded that hyoscine lessened rigidity. In order to overcome the toxic effects of hyoscine, as evidenced by blurred vision and dry mouth, Hurst (11) added pilocarpine nitrate; by the addition of this drug he was able to increase the oral dose of hyoscine up to grain 1/8 without toxic symptoms.

In 1925 Juster (13) published a paper upon the effect of stramonium in abolishing Parkinsonian rigidity. This was followed by a further communication on the subject by Laignal-Levastine and Valence (15). The latter workers recorded the results of a year's trial in cases of encephalitis lethargica. During this period they treated a large number of patients, of whom twenty-four were critically observed and followed up. They used powdered *datura stramonium* in the form of pills, commencing with a dose of 0·1 grm. thrice daily, and increased this gradually until their patients were taking a maximum of 1 grm. of dried stramonium per diem. In cases so treated they noted a marked improvement, evidenced by diminution or abolition of rigidity, of bradykinesia, and of excessive salivation. In some cases they remarked that tremor also disappeared; furthermore, the 'mental' improvement was considerable; the patient, who before treatment was depressed, introspective, and melancholic, became cheerful, alert, and hopeful. These authors gave an account of the toxic symptoms produced by large doses of stramonium, the chief of which were paralysis of accommodation and dryness of the mouth. They attempted to minimize these symptoms by giving the patient alternate periods with and without treatment. This system apparently gave fairly satisfactory results, though it was observed that during the remissions of treatment the rigidity always recurred. Harris (9), when working upon the knee-jerks in post-encephalitic Parkinsonism, tried the effect of tincture of stramonium in 25-minim doses thrice daily: his results were disappointing.

We have found no reports of investigations which compare the value of these drugs and attempt to record instrumentally the effect upon tone, fine movements, and rapidity of movement. In an endeavour to make such a comparison we have recorded graphically (*a*) the time taken to stretch a voluntarily relaxed group of muscles, (*b*) a series of repeated fine movements (ergograph tracing), and (*c*) a simple voluntary movement.

These instrumental observations were made upon five patients with the Parkinsonian syndrome. Four of these cases were post-encephalitics; the fifth was a woman with idiopathic paralysis agitans. In addition we have made clinical observations on a further series of twenty cases in the Out-patient Department; these cases will be referred to again at the end of this paper.

Particulars of the five cases admitted to hospital for instrumental observation are as follows :

Case.	Age.	Onset of Acute Encephalitis.	Onset of Parkinsonian Syndrome.	Observations.
I	35	1920	1922	Rigidity marked. Tremor marked.
II	27	1924	Immediate	Rigidity marked. Tremor marked.
III	28	1921	1923	Rigidity marked. Tremor marked.
IV	20	1923	1926	Rigidity marked. No tremor
V	56	—	1922	Rigidity marked. Tremor marked.

Apparatus and Methods of Recording.

(a) *Stretching of voluntarily relaxed muscles* (*'biceps' and 'triceps' rigidity curves*). The apparatus used for these records is shown in the diagram (Fig. 1). The patient was seated in a chair with the right upper arm firmly fixed by means of a splint, the forearm being fully supinated for the biceps and pronated for the triceps tracing. A strap was fastened round the wrist, and to this were attached cords passing over pulleys. In order to abolish error arising from variations in the length of individual forearms, in each case the cords were attached at a distance of 25 cm. from the internal condyle. The upper cord operated a lever working on a smoked drum, to the lower was attached a weight (1 kilo). The object of this weight, which remained suspended throughout the movement of the arm, was to provide a standard means of stretching a passively relaxed muscle, and the tracings obtained indicated the time taken to do this before and after treatment respectively. Records were taken from the biceps and triceps groups of muscles. In either case the forearm moved through approximately 80°. Before the recording of each movement, the patient was encouraged to relax, and was engaged in conversation in order as far as possible to distract his attention from the investigation in progress. The observer held the patient's arm in the 'zero' position until he judged that relaxation was complete. He then suddenly removed his support, thus allowing the patient's forearm to fall through the given distance. The time taken by the wrist to fall was simultaneously recorded on the drum by means of a tuning-fork registering 1/50ths of a second.

(b) *Repeated fine movements* (*ergograph tracings*). By means of a Mosso's ergograph, tracings were obtained of alternate flexion and extension of the right middle finger over a period of 80 secs. A weight of 300 grm., which was attached to the finger, was just sufficient to keep the string taut, but insufficient materially to tire the patient. The time in seconds was similarly recorded. For purposes of comparison a record was kept of the number of flexions made in the entire 80 secs., in the first 10 secs. and in the last 10 secs. at each observation. The difference between the readings in the first and last 10 secs. gave an indication of the degree of fatigue produced by the movement.

(c) *Speed of voluntary movement ('bradykinesia' tracings).* In Cases II and IV the speed of voluntary movement was further recorded by giving the patient the end of a string to hold, and getting him to pull it down vertically

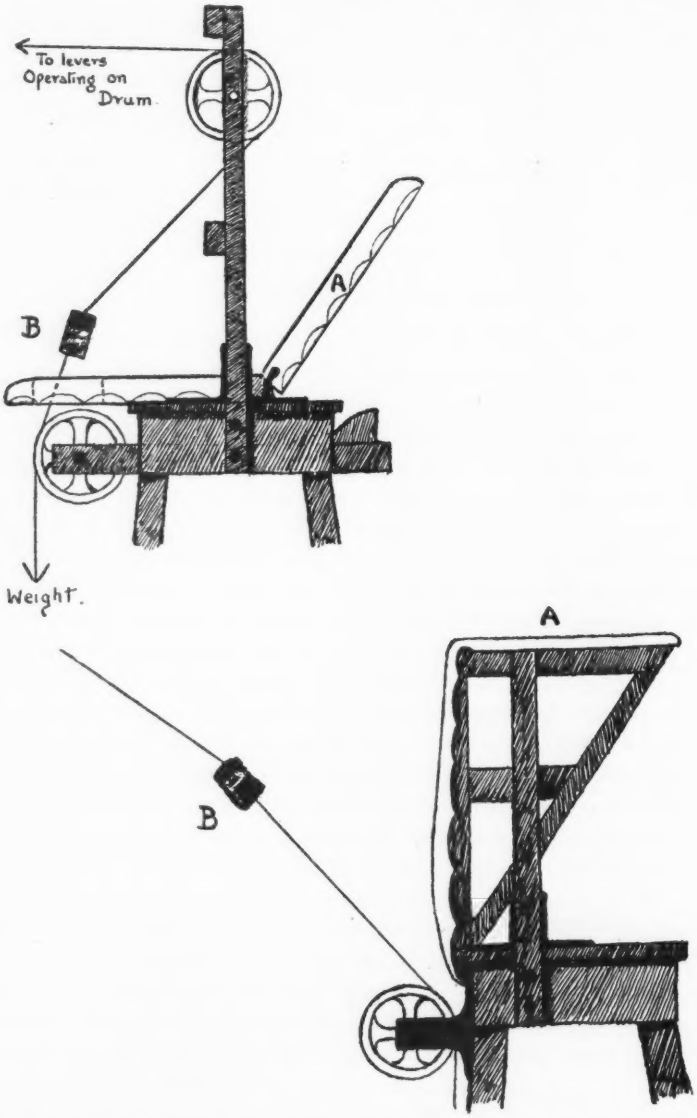


FIG. 1. A. Splint to which upper arm was fastened. B. Wrist strap.

and then let it up through a similar distance. This string passed over a pulley and was attached to a writing arm. The time taken was recorded on the drum in seconds, the excursion of the string being uniform at each investigation. The

patient was allowed to accomplish this movement in his own time, no encouragement being given him to move the string either quickly or slowly. Hall (8) has shown that the bradykinesia of Parkinsonism may be considerably modified by a suitable mental stimulus, and it was found quite early in this investigation that a sharp command to move quickly would result in a considerable augmentation of the patient's ordinary rate. By means of this tracing an attempt was made to obtain some record of his spontaneous rate of movement, and it was found that this could best be obtained by avoiding any suggestion of command and by asking him, almost casually as it were, to pull the string at the required moment. Considering the 'functional' element involved in these tracings, they gave remarkably constant results from day to day in the same patient on a given line of therapy.

It was impossible to obtain satisfactory tracings of tremor which were comparable in different patients and in the same patient from day to day. For this reason any references made to the influence of therapeusis on tremor will be the result of ordinary clinical observation only.

Normal Tracings.

As controls to the results obtained from patients with the Parkinsonian syndrome, 'biceps' and 'triceps' curves and ergograph tracings were taken from a series of normals. The results obtained were as follows:

A normal biceps or triceps curve was smooth throughout and of progressively increasing speed; it lasted a period of 0·26 secs. to 0·38 secs. A typical normal biceps tracing is shown in Pl. 3, Fig. 2.

A normal ergograph tracing showed a series of deflexions uniform throughout in amplitude and in rate. The number of deflexions varied in individual normals with an average of ninety in 80 secs. Further, the number of deflexions recorded in the first 10 secs. was approximately the same as that recorded in the last 10 secs., being on the average eleven.

It was not thought necessary to take controls for the 'bradykinesia' tracings, as the patient in this respect provided a control to himself.

Tracings from Patients with the Parkinsonian Syndrome.

Tracings were taken from each case on two consecutive days before any treatment was commenced. Each drug was then administered separately for a period of a week, during the last two days of which tracings were obtained. After each line of therapy and before commencing a new drug, all treatment was suspended for a week, tracings being taken on the last two days. The figures obtained during these remissions of treatment were in all respects similar to those before any treatment was commenced. For this reason the control figures for each patient remain the same throughout. At each sitting three biceps and three triceps rigidity curves and one ergographic record were obtained. By taking three such tracings on each occasion it was hoped to reduce the experi-

mental error in the rigidity curves to as low a degree as possible. In addition bradykinesia tracings were obtained at each sitting from Cases II and IV. The figures given for the biceps and triceps curves are the average of six tracings, and for the ergographic record of two tracings.

Analysis of Tracings obtained before Treatment.

(a) *Biceps and triceps rigidity curves.* In untreated cases of the Parkinsonian syndrome the rigidity curves were lengthened as compared with the normal. The average durations of the biceps and triceps tracings in individual cases were as follows:

Case.	Biceps. (Normal: 0·26–0·38 secs.)	Triceps. (Normal: 0·26–0·38 secs.)
	secs.	secs.
I	0·84	0·86
II	0·41	0·52
III	0·50	0·58
IV	0·26	0·68
V	1·16	0·91

It will be seen that in four of the cases both biceps and triceps curves showed considerable lengthening; in the other (Case IV) the duration of the biceps curve was within normal limits, though the triceps curve showed obvious prolongation. In four of the cases the curves, instead of being smooth in outline, showed definite interruptions in speed; these interruptions were apparently the graphic record of 'cog-wheel' rigidity. (See Pl. 3, Fig. 3.)

(b) *Ergographic records.* The number of deflexions were fewer than in healthy controls; they were of smaller amplitude; they were irregular in time and amplitude, and definite step-like interruptions were present on the segments of the tracing corresponding to individual flexion-extension movements. The figures obtained were as follows:

Case.	No. of Flexions in 80 secs.	No. of Flexions in first 10 secs.	No. of Flexions in last 10 secs.
I	32	5	2
II	22	4	2
III	26	5	3
IV	51	7	5
V	28	4	3

Furthermore, in the untreated cases the 80-second tracing was frequently interrupted by pauses preceded by flexions of decreasing amplitude, as though the patient had rapidly become fatigued by the movement, although generally when questioned he refused to admit fatigue. These pauses occurred so frequently in the ergographic records that they seemed to form an important and characteristic feature of the Parkinsonian condition. They may be regarded as a manifestation of that sudden abolition of initiative which commonly occurs in this condition, and which in the everyday life of the patient is seen as a tendency to 'stick' at a certain point in dressing himself, or in carrying food to the mouth.

When urged to continue the tracing after one of these pauses, he would generally commence with renewed vigour, the flexions immediately following the pause being generally of considerably greater amplitude and rapidity than those which had just preceded it.

Effect of Drugs.

(1) *Hyoscine subcutaneously.* One patient (Case V) became delirious after a single injection of grain 1/100 of hyoscine hydrobromide; the drug was therefore suspended. This was the patient with idiopathic paralysis agitans. In two of the post-encephalitic cases the effect of hyoscine injections was instrumentally observed. The initial dose was gr. 1/100th of hyoscine hydrobromide given subcutaneously three times a day; after two days this was increased to gr. 1/75 three times a day. The tracings were obtained 1 to 2 hours after the last injection of gr. 1/75. The following table gives the results obtained:

Case.	Average Biceps in secs.	Average Triceps in secs.	No. of Ergograph Flexions. In 80 secs.	In first 10 secs.	In last 10 secs.
I	Before treatment.				
	0·84	0·86	32	5	2
	After hyoscine.				
	0·36	0·40	89	13	9
III	Before treatment.				
	0·50	0·58	26	5	3
	After hyoscine.				
	0·34	0·40	88	13	11

(2) *Hyoscine by mouth.* Two cases (III and IV) were given hyoscine hydrobromide by mouth. Both were given gr. 1/30 thrice daily for several days, after which tracings were taken with the following results:

Case.	Average Biceps in secs.	Average Triceps in secs.	No. of Ergograph Flexions. In 80 secs.	In first 10 secs.	In last 10 secs.
III	Before treatment.				
	0·50	0·58	32	5	2
	After hyoscine.				
	0·30	0·38	88	12	8
IV	Before treatment.				
	0·26	0·68	51	7	5
	After hyoscine.				
	0·29	0·44	82	12	11

(3) *Stramonium.* Tincture of stramonium by mouth was given to all five of these patients. The initial dose in each case was 20 minims thrice daily; this was increased up to 90 minims in two of the patients who showed little or no intolerance to the drug. Two others reached a maximum of 60 minims and 75 minims respectively three times a day, while the third (Case V) was unable to tolerate more than 45 minims three times a day. Below are the figures obtained, with the actual dosage given on the day of each observation.

Case.	Dosage.	Average Biceps in secs.	Average Triceps in secs.	No. of Ergograph Flexions. In 80 secs.	In first 10 secs.	In last 10 secs.
I	Before treatment.	0·84	0·86	32	5	2
	Tr. Stramonii (1) xxx t.d.s.	0·51	0·71	77	12	10
	„ „ (1) xlv „	0·51	0·69	107	15	12
	„ „ (1) lx „	0·42	0·43	129	19	13
	„ „ (1) lxxv „	0·39	0·5	115	17	14
II	Before treatment.	0·41	0·52	22	4	2
	Tr. Stramonii (1) xc t.d.s.	0·28	0·35	70	8	8
III	Before treatment.	0·50	0·58	26	5	3
	Tr. Stramonii (1) xxx t.d.s.	0·36	0·3	50	7	4
	„ „ (1) xlv „	0·24	0·31	63	8	8
	„ „ (1) xc „	0·33	0·31	61	8	7
IV	Before treatment.	0·26	0·68	51	7	5
	Tr. Stramonii (1) lx t.d.s.	0·23	0·33	100	12	11
V	Before treatment.	1·16	0·91	28	4	3
	Tr. Stramonii (1) xv t.d.s.	0·93	0·85	45	8	5
	„ „ (1) xxv „	0·34	0·41	51	8	7
	„ „ (1) xlv „	0·32	0·3	64	10	8

It will be seen from the above tables that both hyoscine and stramonium considerably reduced the length of the rigidity curves in each of the patients in which they were tried. The curves became smooth in contour, losing their 'cog-wheel' features. These instrumental observations coincided with a marked clinical improvement in the rigidity of the arm muscles. The ergograph tracings showed a more remarkable change in the direction of the normal; the number of flexions in 80 secs. came to equal or even exceed the average normal; the tracings lost their step-like interruptions and became normal in form and amplitude (see Pl. 3 and 4, Figs. 4 and 5); the pauses, which had been a feature of tracings taken before treatment, under treatment generally disappeared. The bradykinesia tracings, which unfortunately were only obtained from two cases (Cases II and IV), showed a corresponding improvement. The figures obtained for these tracings before and after treatment were as follows:

Bradykinesia Tracings.

Case.	Before Treatment.		Hyoscine hydrobromide.		Tinct. Stramonii.	
	Up. secs.	Down. secs.	Up. secs.	Down. secs.	Up. secs.	Down. secs.
II	2·0	2·0	1·8	1·6	1·3	1·2
IV	7·9	8·6	2·9	4·0	1·7	2·2

The improvement in the ergograph tracings obtained in Case I after injections of hyoscine was so striking that at first we were inclined to attribute some of it to 'psychic' effect, since the patient believed that she was having a new remedy. In order to obtain evidence on this point the hyoscine injections were suspended and the patient given injections of distilled water from a similar bottle. Within three days a complete relapse occurred, the ergograph and rigidity curves reverting to the untreated state. Ergograph tracings from this patient, before treatment, on hyoscine injections, on distilled water injections, and on tincture of stramonium, are shown in Pl. 4, Fig. 6.

We have found throughout our investigations that as regards both hyoscine and stramonium therapy, cessation of treatment for even a few days is sufficient to produce a complete relapse in each type of curve. This is only to be expected, since the treatment is at best a palliative one for an incurable disease.

Comparison of Therapeutic Effects of Hyoscine and Stramonium.

1. *Instrumental observations.* As regards the instrumental records alone there would seem at first to be little to choose between these three lines of therapy; any one of them in adequate dosage would convert the tracings almost to normality. Stramonium by mouth had a more beneficial effect upon the ergograph tracings than had hyoscine, either by mouth or subcutaneously. The hyoscine tracing might be nearly as rapid as the stramonium tracing, but tended to be less regular in time and amplitude; this is well shown in Fig. 6. The rigidity curves gave results slightly in favour of stramonium, but the essential superiority of stramonium over hyoscine medication lay in a comparison of the clinical picture with the instrumental records.

2. *Clinical observations.* In addition to the five patients admitted to hospital for instrumental observations, twenty patients were treated with hyoscine and with stramonium in the Out-patient Department. Seventeen of these were post-encephalitic cases: the other three were elderly patients with idiopathic paralysis agitans. Both hyoscine and stramonium had considerably less beneficial effect in these three patients than in the others; further, the older the patient the more susceptible to toxic symptoms he appeared to be. The two oldest of our patients with paralysis agitans were unable to tolerate even 25 minims of tincture of stramonium by mouth, and the benefit obtained by giving smaller doses of this drug was practically negligible. In the case of the younger post-encephalitic patients, very large doses of stramonium were well tolerated, and in every case clinical improvement was observed.

In some of the patients the improvement was dramatic. Cases I and III were admitted to hospital bed-ridden; before treatment they had to be fed and washed, and their nursing occupied much time of the ward staff; they had constant dribbling from the mouth, After a few doses of stramonium they became less dependent upon the nursing staff, and on full dosage they were able to get up and dress themselves and even help in the ward routine; the dribbling of saliva ceased, while mentally they became more alert and cheerful. Each one of the patients has remarked that on stramonium he or she has felt enormously 'better': this corresponds with the experience of the French observers who used this drug. On physical examination of the patients treated with stramonium, the following points were noted: the face became less mask-like, and the facility of expressional movements to some extent returned: the attitude became less stooping: the ability to get about improved: rigidity was in all cases diminished, and the range of voluntary power increased: incidentally, as stated, the mouth became dry and dribbling ceased, while it was noted that the skin became less greasy.

On the other hand, tremor appeared to be little, if at all, affected by the drug; in two cases it became slightly more evident under treatment.

Two examples of marked improvement under stramonium treatment seem worthy of special mention. One is a woman who was carried into hospital on a stretcher: she had for months been incapable of doing anything for herself. She has now been taking tincture of stramonium, minims 75, thrice daily for a year; she does her own housework and even manages to earn a living as a laundress. The other is a girl who, on account of disability, had lost her secretarial post in the City; she is now back at work, and a few weeks ago was promoted on account of her capabilities as a typist.

Comparing these results with the effects of hyoscine, it was found impossible to produce similar subjective or objective improvement with hyoscine by mouth. Hyoscine subcutaneously gave very similar effects, but they were more evanescent than those produced by stramonium treatment. Further, hyoscine in the large doses necessary to produce such effects was apt to cause mild delirium; in two in-patients it had to be stopped on the request of the hospital sister, as the patient's exuberant expletives were causing annoyance in the ward. The toxic effects of stramonium, though similar to those of hyoscine, seemed to be much less, and the patient who was taking sufficient stramonium to produce normal tracings was generally untroubled by severe toxic symptoms. Even Case V, who was quite intolerant of hyoscine, was able to take 45 minims of tincture of stramonium thrice daily without ill effect other than slight xerostomia. The undesirability of repeated subcutaneous injections is a further point against the use of hyoscine in the Out-patient Department.

We have therefore come to the conclusion that stramonium, as a method of palliative treatment, is more potent than hyoscine by mouth, and possesses obvious advantages over hyoscine subcutaneously.

Dosage and toxic effects of stramonium. Unlike the French observers who used powdered stramonium leaves in pills, we have adhered almost entirely to the tincture of stramonium in these investigations. Two out-patients were treated for a short time with a dry preparation of this drug, but the results were disappointing. Each patient has received stramonium in dosage varying from 20 to 90 minims of the tincture by mouth thrice daily. The initial dose given has usually been 20 minims. In two patients the effects of increasing dosage have been observed graphically: charts are appended showing the results (Fig. 7); it is obvious from these that in order to obtain the maximal beneficial effects of the drug it is necessary to give doses far above the pharmacopoeial upper limit (15 minims). The dose could be increased daily till the optimum was reached. The best results were obtained with doses of 45 to 60 minims thrice daily; beyond that level no further improvement usually occurred, and in two cases a definite regression took place in the ergograph tracings and rigidity curves, when the dosage was increased up to 75 and 90 minims. This was confirmed by experience in the Out-patient Department, though the optimum dose varied somewhat in individual cases. Once the optimum dose has been found, the patient can be

kept at that level apparently for an indefinite period with constant relief of symptoms. Case I in the instrumental series has taken 75 minims thrice daily for over a year, and, as stated above, she is now able to earn a living as a laundress. She is quite untroubled by toxic symptoms.

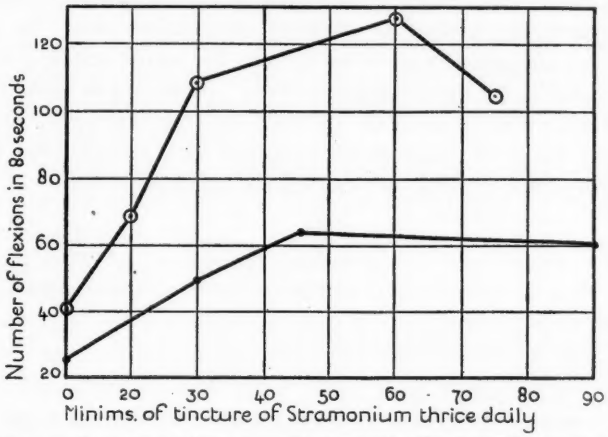


FIG. 7. Ergograph tracings taken at weekly intervals after 6 and 7 days on each dose.

The toxic effects of stramonium vary in intensity from case to case, but the age of the patient seems to have a definite bearing upon them. The elderly patients with idiopathic paralysis agitans appear to be more intolerant of the drug than the younger post-encephalitics. The youngest patient so far treated, a boy of 12, has taken 60 minims of the tincture thrice daily for several months without any adverse effect.

In patients susceptible to the drug, toxic symptoms may appear with any dosage over 30 minims thrice daily; the first symptom usually complained of is blurred vision; next come dryness of the mouth, nausea, and occasional vomiting. Two patients developed attacks of diarrhoea, but these ceased on a reduction of the dose. The pulse-rate was unaffected in all; in no case was delirium produced, nor was any toxic rash seen. It was observed that during the early stages of this treatment all the patients lost weight; after a period of time this ceased and weight was ultimately gained. It will be seen that compared to those of hyoscine, the toxic effects of stramonium are on the whole mild. The most striking testimony to their mildness is afforded by the fact that when, owing to the development of nausea, the drug has been suspended, the patient has almost invariably asked that it be restored.

It has been found possible to mitigate the poisonous effects of stramonium in various ways. The blurred vision, due to pupil dilatation, is considerably relieved by the daily instillation of one drop of $\frac{1}{4}$ per cent. eserine into each eye; it is sometimes sufficient to do this every other day. The dryness of mouth and fauces was combated by giving 'Thirst-quencher' tablets (Burroughs, Wellcome & Co.), to be slowly dissolved in the mouth: a few patients found relief by the addition

of tincture of jaborandum to the stramonium mixture. It was found that in most cases this distressing symptom became better tolerated by the patient as time passed. Nausea and vomiting were usually only relieved by lessening the dosage of stramonium; it was found, however, that careful attention to the bowels and avoidance of constipation somewhat abated these symptoms.

Comparison of therapeutic effects of stramonium and its individual alkaloids. An attempt was made to find out the active principle of the stramonium responsible for these beneficial effects. According to Cushny the active principle of stramonium is an alkaloid which is isomeric to atropine. Comparative tracings were therefore made under treatment with atropine and laevo- and dextro-rotatory hyoscyamine. The results are tabulated below:

Case.		Average Biceps in secs.	Average Triceps in secs.	No. of Ergograph Flexions. In 80 secs.	In first 10 secs.	In last 10 secs.
II	Tincture of stramonium	0·28	0·35	70	8	8
	Atropine, 1/33 gr., hypodermically, t.d.s.	0·34	0·41	44	6	5
	Dextro-rotatory hyoscyamine, 1/6 gr., hypodermically, t.d.s.	0·41	0·57	30	6	3
	Laevo-rotatory hyoscyamine, 1/33 gr., t.d.s.	0·40	0·38	45	6	6
IV	Tincture of stramonium	0·23	0·33	100	12	11
	Atropine, 1/33 gr., hypodermically, t.d.s.	0·36	0·42	67	9	8
	Atropine, 1/33 gr., by mouth, t.d.s.	0·35	0·42	50	7	6
	Dextro-rotatory hyoscyamine, 1/20 gr., hypodermically, t.d.s.	0·36	0·48	58	9	7
	Laevo-rotatory hyoscyamine, 1/33 gr., t.d.s.	0·32	0·48	48	6	6

Dextro-rotatory hyoscyamine, a difficult alkaloid to obtain pure, was kindly supplied by Dr. Trevan of the Burroughs Wellcome Laboratory, to whom we tender our thanks. The crystals were dissolved in doubly distilled water, and this solution was tested for its activity by counting the pulse-rate following hypodermic injection; gr. 1/20 was found to slow the pulse by about 10 beats per minute eight to twelve minutes after injection. On account of this action it was presumed that the solution remained unracemized.

The effect of these pure alkaloids was not in any way comparable to that of tincture of stramonium. Atropine in doses of gr. 1/33 appeared to be the most efficient. The dosage of each drug was increased until the patient showed toxic symptoms, at which stage tracings were taken. By this method the maximum dose capable of being given to any one case was obtained. In addition to these two patients on whom instrumental observations were made, five out-patients have been treated with the various alkaloids of stramonium given individually by mouth. In none of them did any single alkaloid produce a therapeutic effect comparable to that of tincture of stramonium. This investigation, though carried out on only a few patients, suggests that the tincture of stramonium contains

active principles as yet unrecognized, or that it is made up of a combination of known alkaloids, which combination produces a better effect than any of its components.

Conclusions.

1. Tincture of stramonium in large doses lessens the Parkinsonian rigidity and increases the ability to perform fine rapid movements as graphically recorded.

2. It appears to improve the mental condition of the patient.

3. It does not affect the tremor.

4. It is at least as efficient as subcutaneous hyoscine in large doses, is better than hyoscine by the mouth, and may be given continuously over a long period of time.

5. The optimum dosage necessary to produce this effect varies in individual cases, though it commonly lies between 45 and 60 minims thrice daily.

6. Toxic symptoms even with this large dosage are rarely severe; they may be combated in various ways; they appear to be more common in elderly patients with idiopathic paralysis agitans, than in the younger post-encephalitics.

7. The whole tincture of stramonium is more efficacious than atropine or laevo- and dextro-rotatory hyoscyamine.

8. The action of stramonium is palliative and not curative.

We desire to express our indebtedness to Professor Fraser for his kindness in allowing us to carry out this work on the Medical Unit, and for his keen interest and practical suggestions. To Dr. Morley Fletcher and Dr. Thursfield we desire to express our thanks for permission to take tracings from patients under their care, and for much help and encouragement.

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FIG. 2. Normal biceps tracing

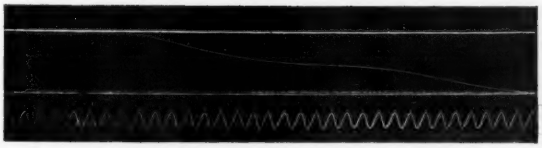


FIG. 3. Biceps curve from untreated case



FIG. 4 Ergograph tracings from Case II
Above—Before treatment. Below—On stramonium



FIG. 5. Ergograph tracings from Case V
Above—Before treatment. Below—On stramonium

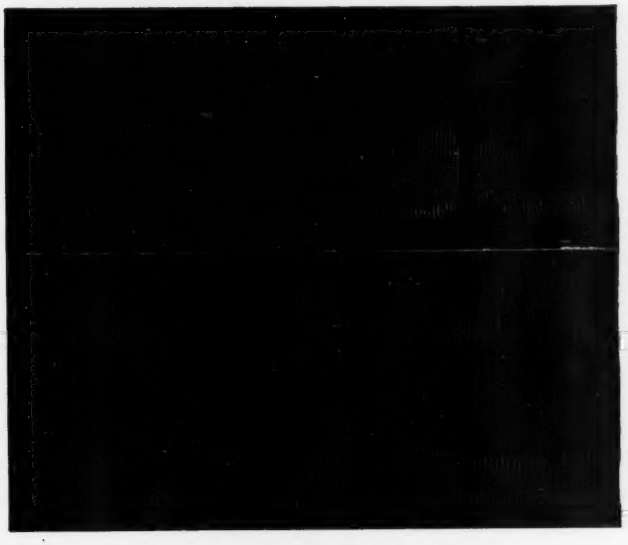


FIG. 6. Ergograph tracings from Case I
A. Before treatment. B. On hyoscine injections. C. On distilled water injections. D. On stramonium



THE DISTRIBUTION OF ELECTROLYTES IN HAEMOPHILIC BLOOD [1]

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A deficiency in the clotting properties of the blood is pathognomonic of haemophilia, but the individual elements involved in coagulation are evidently present in normal quantities. This has led several investigators to perform a detailed analysis of the blood chemistry in this disease. The results of these investigations have revealed no abnormality apart from what would appear to be some disturbance in the distribution of chlorides. Opitz and Zweig (9) observed that the chloride content of the whole blood was abnormally high. This was confirmed by Reimold, Stöber, and Klinke (10), and by Klinke (7), who also found that the blood potassium content was elevated. Since the analyses were on whole blood, it is possible that the deviations from usual composition may have been due to variations in the cell content.

Christie, Davies, and Stewart (2), in a study of various factors in haemophilic blood, determined the CO_2 absorption curves in two such bloods, and the Cl content of the true plasma centrifugalized after saturation with varying tensions of CO_2. They found that the bicarbonate content of the plasma increased with increasing CO_2 tension, quantitatively as in normal blood. But the Cl content did not diminish. In normal blood the increase in plasma HCO_3 is due to migration of an equivalent of Cl anions into the cells, leaving base free to combine with CO_2 (Doisy and Eaton (3); van Slyke, Wu, and McLean (1923)). Because there was no evidence of such Cl migration, Christie, Davies, and Stewart drew the logical conclusion that the increase of plasma $BHCO_3$ with increasing CO_2 tension in whole blood must be due, in haemophilic blood, to migration of alkali out of the cells, a phenomenon which normally does not occur to a measurable extent. Doisy and Eaton (3) and van Slyke, Wu, and McLean (1923) found that when allowance in calculations was made for the water shift between cells and serum that accompanies CO_2 tension change, the Cl shift entirely accounted for the HCO_3 change in true serum. Furthermore Wakeman, Eisenmann, and Peters (16) found that when the electrolyte content of human blood was changed by moderate dilution with water, or by addition of the chlorides and bicarbonates of Na and K, no migration of either Na or K across the cell wall could be discovered by quantitative analysis. Wakeman, Eisenmann, and

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Peters pointed out possible sources of error in similar experiments of Hamburger (4), which led that author to the conclusion that the cations do readily migrate across the uninjured red cell membrane. This conclusion of Hamburger's appears untenable in view of the subsequent results of the above investigators.

Recently Hastings, Sendroy, and van Slyke (5, 6) have analysed a series of thirty pathological bloods, from patients with pneumonia, nephritis, diabetes, acute arthritis, and cardiac disease, and found no abnormality in the distribution of Cl and HCO_3 between cells and serum in any of them.

The unusual nature of the findings which have been recorded concerning the blood chloride in haemophilia made a confirmation appear important. With some difficulty we have secured a case of haemophilia, and have studied his blood. Although material for only one experiment could be obtained, the results appear conclusive in showing an entirely normal serum chloride and bicarbonate concentration, and a normal shift of Cl and HCO_3 anions with changing CO_2 tension.

Case History.

A. M. M., male negro half-caste. Aged 26 years.

Family history. One brother died from haemorrhage following tonsillectomy. One brother died of pneumonia one year ago, giving history of bleeding from trauma and of spontaneous haemorrhages from nose and gums and into joints. One brother alive. Bleeds readily from the slightest trauma, and has spontaneous haemorrhages from gums and nose and into joints. Two sisters alive and well. No history of haemorrhagic tendency. Both unmarried. No history of any haemophilic tendency in previous generations.

Personal history. Since infancy has suffered from haemorrhages from the kidney, bowel, nose, and gums, and into his joints. Haemorrhage from cuts has always been obviously abnormal. He has been in two hospitals, and in both his blood was examined and a diagnosis of haemophilia made. His last severe haemorrhage was into the right knee, two months ago, but he had slight bleeding from the gums on the morning of the day blood was taken for analysis. Coagulation time 110 and 95 minutes (Howell's method in duplicate at 22° C.). Fragility of corpuscles normal. Blood group: Group A. B. (Jansky Group IV), M negative, N positive, P positive (1).

The patient then presents the complete clinical picture of haemophilia. This disease has been shown to occur in American negroes (2), and the family history, the personal history, and the coagulation time of the blood leave no doubt as to the diagnosis.

Methods.

Saturation. Three portions of blood were saturated at 38° C. with air containing approximately 25, 60, and 200 mm. of CO_2 tension. The saturation technique of van Slyke, Wu, and McLean (1923) was employed. After the saturation the blood was drawn into a centrifugalizing vessel under oil, the oil was replaced by paraffin, and the blood was centrifugalized. The technique throughout the handling of the blood and the separation of the cells and serum was that of van Slyke, Wu, and McLean, likewise the procedure for determining

the CO_2 tension by Haldane analysis of the gas phase after it had been separated from the blood.

Water was determined in serum by drying 1 c.c. weighed samples to constant weight at 110° C. The serum sample could be measured accurately in a pipette so that the water content was determined both per unit volume and per unit weight. The cells could not be measured accurately by volume, so that only water content per unit weight was determined.

CO_2 *in serum* was determined in 1 c.c. samples by the manometric apparatus of van Slyke and Neill (13). Measured by weight, the stop-cock pipette was weighed when filled with cells, and again after the sample had been delivered into the chamber of the manometric apparatus.

CO_2 *in cells* was determined in weighed samples as follows. Six c.c. of N/60 lactic acid were placed in the chamber of the manometric apparatus, and all the dissolved gases were extracted and ejected. This procedure removed the slight but measurable trace of CO_2 present in distilled water. About half of the extracted lactic acid solution was run up into the cup of the chamber, and the sample of approximately 1 c.c. of cells was delivered directly into the chamber from a rubber-tipped, stop-cock pipette, as shown in Fig. 4 of van Slyke and Neill. The water in the cup above the chamber was then run into the latter, washing through the drop of cells in the connecting capillaries. With 7 c.c. of fluid in the chamber, the CO_2 was extracted, and was measured by absorption with gas-free 1/N NaOH, as described by van Slyke and Neill for whole blood. The cell sample was measured by weight, the pipette being weighed before and after delivery of the sample. The results in millimols of CO_2 were calculated with the factors of Table X of van Slyke and Sendroy (14).

Chlorides were determined in weighed samples of serum and cells by the method of van Slyke (12); in the procedure the serum or cells were mixed with three volumes of concentrated nitric acid containing a known amount of silver nitrate, and heated until the organic matter was destroyed and the chloride precipitated as AgCl. The excess silver in solution was then titrated with sulphocyanate. A test of this method on serum and cells of various animal species, carried on in the laboratory of Professor D. Wright Wilson in Philadelphia, and of van Slyke in New York (unpublished), has shown that in an occasional abnormal human serum, for a reason not yet identified, this method yields results 1 or 2 per cent. too low. In sera which gave low results, correct ones were obtained when the silver nitrate in water solution was mixed with the serum before nitric acid was added. This improvement, due to Professor Wilson, had not been introduced at the time the present work was done. The possible error of the original method is, however, not sufficient to be of significance in interpretation of our results.

Calculations.

Concentrations of CO_2 and Cl were calculated in millimols per kilo of H_2O, in accordance with the procedure of van Slyke, Wu, and McLéan (1923). The

CO_2 tension was calculated from the CO_2 content of the tonometer air, diluted with a known volume of room air, as described by van Slyke, Wu, and McLean. The concentration of physically dissolved CO_2, symbolized as H_2CO_3, was calculated from the CO_2 tension by the formula

$$\text{Mm. } H_2CO_3 \text{ per kg. } H_2O = \frac{\alpha^\circ p}{22{\cdot}26 \times 0{\cdot}76},$$

in which p represents CO_2 tension, and α° represents the solubility of CO_2 in terms of c.c. of the gas, measured at 0° C., 760 mm., dissolved per gram of water in serum or cells. The value of α° has been recently determined by van Slyke, Sendroy, Hastings, and Neill (15) to be 0·553 for serum and 0·60 for cells; these values were employed, making the H_2CO_3 calculations:

$$[H_2CO_3]_{\text{serum}} = 0{\cdot}0327\ p.$$
$$[H_2CO_3]_{\text{cells}} = 0{\cdot}0354\ p.$$

Bicarbonate was calculated as the difference between total CO_2 and physically dissolved CO_2.

$$[BHCO_3] = [CO_2] - [H_2CO_3].$$

Serum pH was calculated by Hasselbalch's equation—

$$pH = pK' + \log \frac{[BHCO_3]}{[H_2CO_3]}.$$

The value of pK′ used was 6·10, which was recently found by Hastings, Sendroy, and van Slyke (5, 6) to be valid when their value for α°, employed in this paper, was used to calculate $[H_2CO_3]$ from the CO_2 tension. (If Bohr's (1) solubility coefficient for CO_2 in serum at 38° C. were used, the corresponding value for pK′ would be 6·13, instead of 6·10.)

Results.

The results of our determinations are given in the two tables on p. 70. Since the decisiveness of the answer to the question at stake depends upon the accuracy of the results, we have in Table I presented all the data of our duplicate analyses. In Table II the mean results are summarized, with the calculated distribution ratios for Cl and HCO_3, and the serum pH.

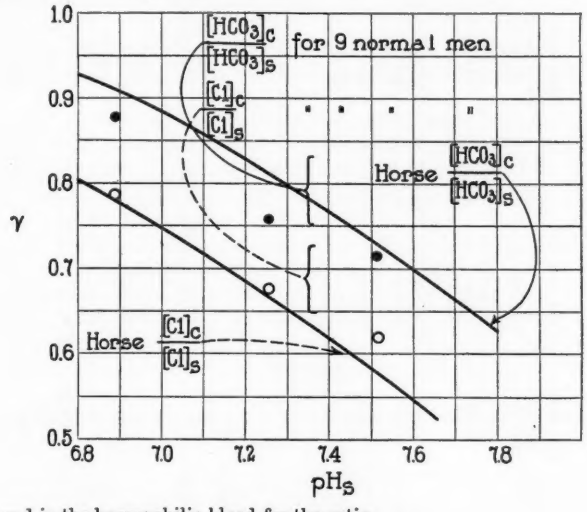
In the chart on p. 69 we have plotted our results with the haemophilic blood, together with curves representing the results obtained by van Slyke, Hastings, Murray, and Sendroy (1925) in experiments by the same technique with oxygenated horse blood. We have also indicated the range of chloride and bicarbonate ratios found by Hastings, Sendroy, and van Slyke (5, 6) in a series of normal human bloods. It is obvious from this chart that:

1. The chloride and bicarbonate distribution ratios in the haemophilic blood are quite within the range for normal blood, although on the lower edge of it.

2. With fall in pH caused by increasing CO_2 tension the chloride and bicarbonate distribution ratios rise, chloride passing into the cells, in practically the same proportions observed by van Slyke, McLean, and Wu (1923) and by van Slyke, Hastings, Murray, and Sendroy (1925) in horse blood.

The mechanism governing the electrolyte distribution between cells and serum in this specimen of haemophilic blood appears to be entirely normal.

We are inclined to attribute the divergence between our results and those of Christie, Davies, and Stewart to differences in technique, in either the handling or the analysis of the blood. The only obvious difference is that the above authors treated their blood with fluoride and oxalate, while we defibrinated instead of adding anticoagulants.



Values found in the haemophilic blood for the ratio

$$\frac{[BHCO_3] \text{ per kilo } H_2O \text{ in cells}}{[BHCO_3] \text{ per kilo } H_2O \text{ in serum}}$$

are indicated by •

Values found for the ratio $\frac{[Cl] \text{ per kilo } H_2O \text{ in cells}}{[Cl] \text{ per kilo } H_2O \text{ in serum}}$ are indicated by O.

The two curves represent the values for these ratios obtained in horse blood by van Slyke, Hastings, Murray, and Sendroy (1925).

The heavy brackets indicate the range in the values of these ratios found in the bloods of nine normal young men by Hastings, Sendroy, and van Slyke (5, 6).

The results from thirty bloods taken from human subjects in other pathological conditions, with similar ones of Hastings, Sendroy, and van Slyke (5, 6), emphasize the probability that conditions causing marked abnormality in the distribution ratios of chloride and bicarbonate between serum and cells in blood are rare, presumably much more so than conditions which alter the general concentration levels of these anions in the whole blood.

Conclusions.

As the result of analyses of both serum and cells separated from blood after saturation with CO_2 at tensions from 25 to 197 mm., we have found entirely normal shifts of Cl and HCO_3 between the cells and serum in a case of haemophilic blood. The serum and cell chloride contents at physiological CO_2 tension were also quite normal.

TABLE I.

CO_2 Tension.	*Analyses of Cells.* H_2O.	CO_2.		Cl.		*Analyses of Serum.* H_2O.		CO_2.		Cl.	
Mm.	Grm. per Grm. Cells.	Mm. per Kg. Cells.	Mm. per Kg. Cells H_2O.	Mm. per Kg. Cells.	M. Eq. per Cell H_2O.	Kg. Grm. per c.c. Serum.	Grm. per Grm. Serum.	Mm. per 1 Serum.	Mm. per Kg. Serum H_2O.	M. Eq. per Kg. Serum.	M. Eq. per Kg. Serum H_2O.
25·0	0·668	10·83	16·21	46·2	69·2	0·930	0·911	20·38	21·90	103·1	113·2
	0·668	10·57	15·82	47·2	70·7	0·930	0·911	20·39	21·92	103·3	113·4
	—	10·71	16·03	—	—	—	—	—	—	—	—
61·4	0·677	16·33	24·13	51·4	76·0	0·927	0·910	28·62	30·90	100·7	110·8
	0·676	16·21	23·95	50·6	74·8	0·925	0·908	28·62	30·77	101·0	111·1
197·1	0·685	28·70	41·90	57·5	84·0	0·923	0·908	42·60	47·17	96·9	106·7
	0·684	28·73	41·95	57·5	84·0	—	—	42·57	46·14	96·8	106·8

TABLE II.

Distribution of Chloride and Bicarbonate between Cells and Serum of Haemophilic Blood at Varying CO_2 *Tension.*

	$[H_2O.]$	$[H_2O.]$	CO_2 Tension.	$[H_2CO_3.]$	$[CO_2.]$	$[BHCO_3.]$	$[Cl.]$	Ratio $\frac{[Cl.]_c.}{[Cl.]_s.}$	Ratio $\frac{[HCO_3]_c.}{[HCO_3]_s.}$	$pH_s.$
	Grm./c.c.	Grm./Grm.	Mm.	Mm./Kg. H_2O.	Mm./Kg. H_2O.	Mm./Kg. H_2O.	M. Eq./Kg. H_2O.			
1. Serum cells	0·930	0·911	25·0	0·818	21·92	21·10	113·3	0·617	0·717	7·511
	—	0·668	25·0	0·887	16·03	15·14	69·9			
2. Serum cells	0·926	0·909	61·4	2·008	30·90	28·89	111·0	0·678	0·758	7·258
	—	0·677	61·4	2·176	24·05	21·87	75·4			
3. Serum cells	0·923	0·908	197·1	6·45	46·16	39·71	106·7	0·787	0·880	6·890
	—	0·685	197·1	6·99	41·96	34·97	84·0			

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AN INVESTIGATION OF PRIMARY LOBAR PNEUMONIA IN MANCHESTER, 1925–7[1]

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Introduction.

In connexion with a study of the bacterial flora of the human nasopharynx, carried out in Manchester during the years 1925–27, the results of which have not yet been published, an opportunity was presented for a combined clinical and bacteriological investigation of a considerable series of cases of pneumonia, which were admitted to the Manchester Royal Infirmary during those years. The present report deals with a series of 193 cases, 116 of which have been studied from both points of view.

The Present Position in regard to Pneumonia.

John Hay (1) recently referred to acute lobar pneumonia as a self-limiting disease tending to recovery. 'In 100 cases,' he says, 'the chances are that about 75 will survive if allowed to do so; 10 to 15 will probably die, doomed from the first. This leaves another 10 to 15 patients, whose chances of recovery will depend on the manner in which the case is handled. The medical man is the determining factor in this small percentage of patients.' While there is a considerable amount of truth in this statement, such a state of affairs seems but a poor return for the efforts of many years of research and must only serve as a stimulus to further work. A new era was opened up by the work of Neufeld and Händel (2), Lister (3), and at the Rockefeller Institute by Dochez and Gillespie (4), Stillman, and others. Their differentiation of pneumococci into types based on the production of specific agglutinins, precipitins, and protective bodies directed new lines of thought and new work, which have continued up to the present date, in an effort to produce an efficient serum treatment for the disease. The original investigators at the Rockefeller Institute described three constant types, I, II, and III, comprising about 80 per cent. of all strains encountered in patients with pneumonia and representing apparently fixed parasitic types. The other twenty per cent. were placed in a 'scrap heap' or 'waste basket'—Group IV—and it was thought that each individual strain of pneumococcus in Group IV was immunologically distinct. The work of Olmstead (5) in 1917 showed that certain strains in Group IV might have common characteristics.

[1] Received June 27, 1928.

Lister found some difficulty in correlating the strains in South Africa with those described by the Rockefeller workers, and thus described several new strains. In an analysis of the organisms isolated from seventy-seven cases of pneumococcal infection, Urquhart (6) contrasted the types described by the Rockefeller Institute with those by Lister. He concluded that the pneumococci responsible for lobar pneumonia and other serious pneumococcal infections in this country were similar to those found in America and in South Africa. Further work at the Rockefeller Institute by Avery (7) rendered necessary a further sub-grouping of the types.

Nicolle and Debains (8) undertook on a new basis the investigation of the agglutination of the types of pneumococci. They concluded that the pneumococcal types of various authors—'antigenic types'—are demonstrable only by the agglutination test; that is, that the types of pneumococci are essentially agglutination types. Reports of the results of pneumococcal typing are forthcoming from most countries in the world (9, 10, 11, 12, 13, 14, 15, 16), and show the varying results of different observers and the difficulties encountered by workers in repeating the experiments of their predecessors in their own and different countries. It thus becomes abundantly clear that universal dogmatic statements about the various types, their incidence, virulence, mortality, relation to clinical details, are not yet warranted.

Apart from the great value which has resulted from the treatment of Type I pneumonia by Type I anti-pneumococcal serum, it is claimed by recent American workers that the results of typing give very valuable information in relation to the diagnosis and prognosis of lobar pneumonia. It was for us to see whether these statements were applicable to the types found in this country.

Review of the literature constantly brings out the difficulties unnecessarily introduced by workers who refrain from giving adequate information as to the source of their material. This is of especial importance in pneumonia—a disease which in some form or other attacks all classes and all ages. Another great difficulty, which is constantly presented, is an inadequate description of the variety of pneumonia with which an author is dealing. This is partly due to the extraordinarily unsatisfactory classifications of the various forms of pneumonia. Many classifications are absolutely futile and make 'confusion worse confounded'. Thus Aufrecht classifies pneumonias as croupous, catarrhal, atypical, hypostatic, aspiration, and desquamative, ignoring the fact that atypical pneumonias may be either croupous or catarrhal, and that aspiration pneumonia is simply a septic form of catarrhal pneumonia. Text-books are full of lengthy, misleading classifications of pneumonia, such as: (1) lobar, croupous, or pleuro-pneumonia with sub-varieties of apical, creeping, migratory or wandering, fulminating or lightning, traumatic, central, post-operative, in children, in the aged, in the insane, abortive or latent, terminal, embolic, alcoholic, toxaemic, complicated. (2) Broncho-pneumonia (lobular, catarrhal or capillary bronchitic), primary, secondary, and inhalation, aspiration, or deglutition pneumonia. So numerous and artificial have the subdivisions become, that they no longer serve

any useful purpose. The mode of subdivision has invariably been one of anatomical or clinical origin, or the classification has been based on the characters, macroscopic and microscopic, of the inflammatory exudate and products. We believe that the only satisfactory classification is one with a bacteriological basis; such a division, based on the causal factors, is not only much more scientific, but is more practical and would focus attention on the aetiological factors rather than on the morbid anatomical findings.

The difficulties are further illustrated by masses of published statistics showing the relations of the different varieties and types of pneumonia to age, sex, &c., but the grounds on which the diagnosis of lobar or broncho-pneumonia was based are not made clear. In many cases the diagnosis is definite, but in others the differentiation may be notoriously difficult, and is so very frequently a matter of individual opinion, that no useful purpose can be served by primary division on anatomical grounds. Statements are common, especially in reference to children, such as 'it is often quite impossible to distinguish clinically between lobar and lobular pneumonia, and the absence of sputum makes the diagnosis still more doubtful. The diagnosis is increasingly difficult in regard to the confluent type of broncho-pneumonia, although the broncho-pneumonic inflammation may often be suspected from the history of pre-existing measles, whooping-cough, by its more gradual onset, by the remittent pyrexia, and by the more protracted course' (17). Notwithstanding the preponderance of catarrhal exudation in early childhood, it is still the pneumococcus which plays the principal role in the causation of the disease, whether the inflammation be lobar or lobular in distribution.

Beddard and Eyre, following West, divided broncho-pneumonia into: (1) primary lobular pneumonia; synonyms: pneumococcal lobular pneumonia, primary broncho-pneumonia. (2) Broncho-pneumonia; synonyms: catarrhal pneumonia, capillary bronchitis, secondary lobular pneumonia. Glynn and Digby (18) think it is probable that the lobular is usually an infection with the 'fixed' types and the catarrhal with Group IV.

Further difficulties in nomenclature have been introduced during the recent influenza epidemics, and it has become quite fashionable to diagnose 'influenzal pneumonia' without any very clear idea of what it signifies either clinically or bacteriologically. J. F. Gaskell (19), in the Bradshaw Lecture of 3 November 1927, reported a series of experiments in an endeavour to ascertain the conditions which govern the distribution of pneumonic consolidation, why in one case broncho-pneumonia is produced and in another lobar pneumonia. He considers that his experiments on rabbits show a sufficiently close analogy to be applicable to human disease, and that the estimation of the virulence of the infecting pneumococcus is of the utmost importance. His results offer a delightful solution of many of the difficulties encountered, but it may well be suggested that further research should be directed along these lines in an attempt to elucidate the many problems of 'acute primary pneumonia'.

Sufficient has been said to indicate the difficulties confronting a presentation of

the results of our inquiry in an intelligible and useful manner, and emphasis may be laid on those points, the absence of which has led to misconception and difficulty in the past.

The Present Inquiry

The investigation includes a record of 193 cases of 'primary lobar pneumonia', which were admitted to Manchester Royal Infirmary during two and a half years extending from January 1925 to June 1927. The cases were all essentially primary pneumonias, that is, distinct from the pneumonias secondary to measles, whooping-cough, streptococcal infections or other disease processes, except mild affections of the respiratory tract. The consolidation was lobar in type—the pneumonic process involving the whole or the greater part of a lobe. The similarity between the cases lay in the mode of onset, the general appearance of the patient, and the course of the disease, the mode of termination and complications rather than on the physical signs in the chest. The common factor was the isolation of the pneumococcus from the sputum in all cases. Virulent pneumococci were found in all cases diagnosed clinically as acute primary pneumococcal pneumonia, regardless of the exact nature of the pulmonary involvement.

Important features of the cases were: (1) In 70 per cent. of cases, a definite history of a preliminary period of malaise and then a sudden onset of more severe symptoms. (2) In 90 per cent. of cases, a rigor at the onset. (3) Headache and vomiting in the younger members at the onset. (4) Pain in the chest. (5) Cough. (6) Sputum—rusty in about 50 per cent. of cases. (7) Raised temperature, pulse, and respiration rates. (8) Course of five to ten days. (9) Termination by crisis or lysis. (10) The physical signs in the chest varied considerably, and in many cases the consolidation appeared to involve a half or two-thirds rather than the whole of one lobe; on the other hand, it was not lobular in distribution. The physical signs were atypical (from the point of view of a text-book description) and variable according to the point of commencement of consolidation and the presence or absence of associated bronchial involvement.

There was considerable periodic variation in the severity of the infection. For example, from January to November 1925, the majority of the patients were fairly comfortable throughout the course of the disease and yet the area of lung consolidation was extensive, whereas in February and March 1926 the patients were desperately ill and the physical signs in the chest were not well marked. From January 1925 to November 1925 the details are available of seventy-seven cases of pneumonia, embracing a full history, mode of onset, course of the case, complications, and results. From November 1925 to June 1927 116 cases have been recorded on a special 'inquiry form', which gives information on the following points: name, age, sex, occupation, previous attacks; addiction to alcohol, history of trauma, antecedent cough, other cases in the household, rigor, pain, cough, sputum, dyspnoea, herpes, the lobes involved, the physical signs in the chest, the condition of the tongue, headache, delirium or vomiting, the pulse, temperature, and respiration (four-hourly), the complications, and the result.

During the latter period the bacteriological flora of the sputum has been examined, and a full account of the methods employed is given in the following section. From January 1926 to June 1927 we kept a record of the presence or absence of haemolytic streptococci and Pfeiffer's influenza bacilli, in addition to the type of pneumococcus. An account is given of the general incidence and mortality rate from pneumonia in Manchester over a corresponding period.

It is obvious that some of the discrepancies brought out on comparing the results of previous workers in this field have been due to unintentional case selection. The patients under review in this inquiry were admitted to the Manchester Royal Infirmary—a voluntary hospital, and were drawn chiefly from the lowest middle and poor classes, being largely young and middle-aged adults. Most of them were recommended to hospital because of unsuitable surroundings at home—no case was refused admission. The majority of the children in Manchester district find their way into special children's hospitals, and the older patients either remain at home or are admitted to the Poor Law institutions. These points may seem trivial and irrelevant, but it is most important to know as much as possible about the source of the material under bacteriological examination. In addition, there is ample evidence that one of the most important, if not the most important, factors influencing the death-rate and the variety of pneumonia is age.

Methods employed in the collection and examination of sputum. Instructions were issued to those responsible for the collection of the sputum of the patient, emphasis being laid upon the desirability of obtaining sputum from the deeper air passages and uncontaminated with organisms normally present in the mouth. With this object in view the mouth was first rinsed with warm water and the specimen obtained by coughing directly into a sterile tin provided for the purpose. This air-tight tin was sent to the Laboratory as soon as possible with the particulars of the patient's name, age, sex, duration of illness, and hospital number. As soon as the specimen was received in the Laboratory a preliminary survey was made by preparing and staining films. Gram and Muir's capsule methods were found to be satisfactory and gave some idea of the proportion of pneumococci to other organisms. Films were always kept in reserve for further examination if necessary. The sputum was also plated upon blood agar and Fildes' agar. Blood agar was necessary for the recognition and isolation of haemolytic streptococci (in addition to pneumococci). Fildes' agar was adopted because of its advantage over other media for the growth of Pfeiffer's influenza bacillus. The plate cultures were incubated at 37° C. and examined after 24 and 48 hours. Colonies were picked off, filmed, and, in the case of Pfeiffer's influenza bacillus, the ability to grow on Fildes' medium but not on plain agar was accepted in conjunction with microscopic findings as evidence of identification. The production or non-production of haemolysis and indol was also tested. The actual typing of the pneumococcus was carried out by a method very similar to that used by the Rockefeller workers (12).

A proportion of the sputum was ground in a sterile mortar with 2 to 3 c.c. of sterile salt solution and about 0·5 c.c. of this mixture injected intraperitoneally into a mouse. The mouse invariably died or appeared to be *in extremis* within 18 hours of injection. A necropsy was carried out as early as possible, great care being taken regarding sterility. After the mouse had been pinned on a dissecting board, the skin was stripped off and the abdominal and thoracic surfaces seared with a hot iron. The sternum was next cut through with sterile

instruments and blood agar plate cultures and films prepared from the heart's blood. Fresh instruments were taken to open the peritoneal cavity and similar cultures and films prepared. The films were stained by Gram's method and by Muir's capsule method, and examined for pneumococci. A Pasteur capillary pipette was then taken and the peritoneal cavity washed out with the aid of several c.c. of sterile salt solution,—the washings being delivered into a sterile centrifuge tube. The exudate was centrifugalized slowly for thirty seconds in order to throw down large particles and leucocytes; the turbid fluid was removed to another centrifuge tube and spun down at a high speed for 20 to 30 minutes. The sediment was re-suspended in sufficient salt solution to give a turbidity of proper concentration for agglutination and bile solubility tests. The latter was carried out by delivering into each of two Dreyer's agglutination tubes an equal amount of the re-suspended pneumococci, 0·6 to 0·75 c.c. being the usual amount. Into one tube was delivered 0·25 c.c. of filtered ox bile and into the other 0·25 c.c. of salt solution; this latter tube served as a control. After incubation for one hour at 37° C. the tube containing the bile should be perfectly clear; if this was not so, one drop of 10 per cent. KOH, by producing alkalinity in an acid sample of bile, immediately gave the required result. Typing by the agglutination and precipitation methods was carried out in the usual way by keeping the antigen constant and using the sera in the following dilutions: 1/10, 1/20, and 1/40. The tubes were incubated in a water bath at 55° C. and readings taken at the end of two hours and checked the next morning. The clear supernatant fluid from the second centrifugalization was used as the antigen in the precipitation reaction. In this case the antigen was diluted 1/2, 1/5, and 1/10. These tubes were incubated in a water bath at 37° C. and readings taken at the same time, viz. at the end of two hours and again the following morning. Rarely did a positive reaction in the one not agree with the other, and all strains of pneumococci isolated were subjected to further agglutination tests. Pure cultures were prepared from single colonies of the blood agar plate culture prepared at the necropsy of the mouse, and these were at one time grown in horse serum broth, but at a later date in Hartley's broth; the cultures were killed by the addition of formalin and by heat, and agglutination experiments prepared under similar conditions. Only once did a strain not giving positive reaction at the first typing prove to be a Type I on subsequent testing. It will be observed that the examination was stringent and a pneumococcus not accepted as such unless it proved to be a Gram-positive lanceolate diplococcus, lethal to a mouse, giving haemolysis on blood agar, capsulated when filmed direct from body fluids and soluble in ox bile.

Type sera had previously been prepared by the immunization of rabbits with strains of Type I, Type II, and Type III; the strains having been kindly sent us by Dr. O'Brien during the winter 1924–5. Antigens were prepared by growing on horse serum agar plates, and the growth washed off with sterile salt solution; the emulsion was killed by the addition of formalin and heated at 56° C. for half an hour. The suspension was washed by successive centrifugalizing and finally re-suspended in 0·25 per cent. formalized saline. The same strains of pneumococci were used throughout the inquiry, although different samples of sera were prepared and used, and at a later date the antigens were grown in Hartley's broth, centrifugalized, and re-suspended. The advantage was that thorough washing was not necessary to rid the antigen of any foreign protein, e.g. horse serum. A titre of 1/160 with its homologous organism was considered satisfactory. It may be noted in passing that no attempt to indicate sub-groups II *a*, II *b*, or II *x* was made, neither were any strains subjected to fermentation reactions.

The methods adopted were quite satisfactory for the identification of the causal organism, and it was found that the isolation through the use of a mouse was eminently superior to any method of direct plating. Frequently it would have been difficult to pick off a pure colony of pneumococcus from a primary

blood agar plate culture, and yet the organism was isolated and identified with ease by the injection of the sputum into a mouse. In a few instances only were organisms other than pneumococci found in the peritoneal cavity, and without exception the heart blood gave a pure culture. It will be seen that the earliest time at which a report could be issued as to the type of pneumococcus was 24 hours after the receipt of the sample of sputum.

One of us was enabled to attend the necropsies of some of the fatal cases and collect samples of lung tissue ; at eight necropsies the type of pneumococcus coincided with those of the sputum. On one occasion a Group IV pneumococcus was isolated, whereas a Type I had been previously incriminated.

The Results of the Investigation and Comparison with other Statistics.

Table I shows the age of the patient, the date of onset (the date given is that on which the rigor occurred or on which the pain in the side commenced), the fate of the patient, and the presence or absence of complications.

This information is given in all cases (193). In Cases 78 to 92 inclusive, only the type of pneumococcus isolated from the sputum is recorded, whereas in the remaining cases the presence of Pfeiffer's influenza bacillus and haemolytic streptococcus is also recorded. The signs + or − denote the presence or absence of organisms respectively.

TABLE I.

No.	Age.	Date of Onset.	Lived or Died.	Complications.	Pn. I.	Pn. II.	Pn. III.	Pn. IV.	Pf.	H.S.
1	32	1.1.25	D.	—						
2	20	3.1.25	L.	Delayed resolution						
3	30	3.1.25	L.	—						
4	66	7.1.25	L.	—						
5	43	15.1.25	L.	—						
6	48	30.1.25	D.	—						
7	11	1.2.25	L.	—						
8	18	4.2.25	L.	—						
9	32	4.2.25	L.	—						
10	33	4.2.25	L.	—						
11	18	6.2.25	L.	—						
12	21	8.2.25	L.	—						
13	20	8.2.25	L.	—						
14	20	19.2.25	L.	—						
15	35	22.2.25	L.	—						
16	26	24.2.25	L.	—						
17	44	2.3.25	L.	Delayed resolution						
18	27	9.3.25	L.	—						
19	31	11.3.25	L.	—						
20	25	15.3.25	L.	Otitis media						
21	25	17.3.25	L.	—						
22	28	20.3.25	L.	Pelvic abscess						
23	34	20.3.25	L.	—						
24	14	24.3.25	L.	—						
25	4	26.3.25	L.	—						
26	49	28.3.25	L.	Pericarditis						
27	38	5.4.25	L.	—						
28	46	7.4.25	L.	Non-resolution						
29	32	11.4.25	L.	—						
30	13	13.4.25	L.	—						
31	27	18.4.25	L.	Empyema						
32	41	20.4.25	L.	Arthritis						

TABLE I (*continued*).

No.	Age.	Date of Onset.	Lived or Died.	Complications.	Pn. I.	Pn. II.	Pn. III.	Pn. IV.	Pf.	H.S.
33	33	21.4.25	L.	Pyo-pneumothorax						
34	49	23.4.25	L.	Non-resolution						
35	45	27.4.25	D.	—						
36	24	4.5.25	L.	—						
37	4	11.5.25	L.	—						
38	38	14.5.25	L.	—						
39	25	17.5.25	L.	—						
40	10	17.5.25	L.	—						
41	47	18.5.25	L.	—						
42	24	20.5.25	L.	—						
43	43	20.5.25	L.	Delayed resolution						
44	26	21.5.25	L.	—						
45	44	21.5.25	L.	—						
46	32	24.5.25	L.	—						
47	46	26.5.25	L.	—						
48	64	27.5.25	D.	—						
49	33	30.5.25	L.	—						
50	16	3.6.25	L.	Non-resolution						
51	19	4.6.25	L.	—						
52	26	8.6.25	D.	—						
53	23	10.6.25	L.	—						
54	8	17.6.25	L.	Delayed resolution						
55	35	18.6.25	L.	—						
56	52	29.6.25	L.	—						
57	42	30.6.25	D.	Pneumococcal meningitis						
58	25	3.7.25	L.	Delayed resolution						
59	55	13.7.25	L.	—						
60	39	16.7.25	L.	—						
61	5	16.7.25	L.	—						
62	42	20.7.25	L.	—						
63	22	24.7.25	L.	—						
64	37	26.7.25	L.	Pleural effusion						
65	52	4.8.25	L.	—						
66	16	5.8.25	L.	Non-resolution						
67	45	8.8.25	L.	Non-resolution						
68	34	11.8.25	L.	—						
69	7	7.9.25	L.	—						
70	13	11.9.25	L.	—						
71	42	13.9.25	L.	—						
72	22	19.9.25	L.	—						
73	20	20.9.25	L.	—						
74	17	22.9.25	L.	—						
75	31	25.9.25	L.	Empyema						
76	6	10.10.25	L.	—						
77	28	12.10.25	L.	—						
78	43	7.11.25	D.	Abscess and gangrene	−	+	−	−		
79	50	21.11.25	L.	—	−	+	−	−		
80	47	23.11.25	L.	—	−	−	−	+		
81	42	29.11.25	L.	—	−	−	−	+		
82	29	3.12.25	L.	—	−	−	−	+		
83	38	14.12.25	L.	—	−	−	−	+		
84	22	18.12.25	L.	Phlebitis of leg	−	+	−	+		
85	29	19.12.25	L.	—	−	−	−	+		
86	26	19.12.25	D.	—	−	−	−	+		
87	26	20.12.25	L.	—	−	−	−	+		
88	47	27.12.25	L.	—	−	−	−	+		
89	23	28.12.25	L.	—	−	−	−	+		
90	28	28.12.25	L.	—	−	−	−	+		
91	18	28.12.25	L.	—	−	−	−	+		
92	26	29.12.25	D.	Peritionitis ; pericarditis	−	−	−	+		

TABLE I (*continued*).

No.	Age.	Date of Onset.	Lived or Died.	Complications.	Pn. I.	Pn. II	Pn. III.	Pn. IV.	Pf.	H.S.
93	29	6.1.26	L.	—	−	−	−	+	+	−
94	38	8.1.26	D.	Parotitis	−	−	−	+	−	−
95	16	29.1.26	L.	Empyema	+	−	−	−	−	−
96	44	13.2.26	D.	—	+	−	−	−	−	−
97	33	14.2.26	L.	—	+	−	−	−	−	+
98	20	18.2.26	L.	—	+	−	−	−	+	−
99	23	19.2.26	L.	—	−	−	−	+	+	−
100	20	19.2.26	L.	Empyema; furunculosis	+	−	−	−	+	−
101	16	3.3.26	L.	—	−	−	−	+	+	+
102	34	3.3.26	L.	—	+	−	−	−	+	−
103	18	8.3.26	L.	—	+	−	−	−	+	−
104	43	10.3.26	L.	Empyema	−	−	−	+	+	−
105	24	12.3.26	L.	—	+	−	−	−	−	−
106	22	23.3.26	L.	Empyema	−	−	−	+	+	−
107	20	26.3.26	L.	—	−	−	−	+	+	−
108	55	30.3.26	L.	—	−	−	−	+	−	−
109	71	2.4.26	D.	—	−	−	−	+	−	−
110	44	2.4.26	L.	—	−	−	−	+	−	−
111	26	6.4.26	L.	—	−	−	−	+	+	−
112	32	10.4.26	L.	—	−	−	−	+	−	−
113	24	10.4.26	L.	Empyema	−	−	−	+	−	−
114	19	11.5.26	L.	—	−	−	−	+	+	+
115	35	16.5.26	D.	—	−	−	−	+	+	−
116	48	24.5.26	D.	—	+	−	−	−	+	−
117	25	24.5.26	L.	—	+	−	−	−	−	−
118	38	27.5.26	L.	—	+	−	−	−	+	−
119	56	28.5.26	D.	Empyema	−	−	−	+	−	−
120	64	2.7.26	D.	Pericarditis; endocarditis	+	−	−	−	−	−
121	24	12.7.26	L.	—	−	−	−	+	−	−
122	49	17.7.26	D.	—	−	−	−	+	−	−
123	45	17.7.26	D.	—	−	−	−	+	−	−
124	41	26.7 26	L.	—	−	−	−	+	+	−
125	34	26.8.26	L.	—	−	−	−	+	−	−
126	34	28.8.26	L.	—	−	−	−	+	−	−
127	13	24 9.26	L.	—	+	−	−	−	−	−
128	35	26.9.26	L.	Furunculosis	+	−	−	−	+	+
129	19	15.10.26	L.	—	−	−	−	+	+	−
130	31	22 10.26	L.	—	+	−	−	−	+	−
131	46	24.10.26	D.	Empyema; pericarditis	+	−	−	−	−	−
132	58	27.10.26	L.	—	+	−	−	−	+	−
133	23	27.10.26	L.	—	+	−	−	−	+	−
134	25	30.10.26	L.	—	−	+	−	−	−	−
135	35	2.11.26	L.	—	−	+	−	−	+	−
136	18	3.11.26	L.	Delayed resolution	+	−	−	−	−	−
137	43	29.11.26	L.	—	+	−	−	−	−	−
138	50	4.12.26	L.	Empyema	+	−	−	−	−	−
139	22	9.12.26	L.	Empyema	+	−	−	−	+	−
140	40	18.12.26	D.	—	+	−	−	−	+	−
141	59	23.12.26	L.	—	−	−	−	+	−	−
142	38	23.12.26	L.	—	−	−	−	+	+	−
143	67	28.12.26	D.	—	−	−	−	+	−	−
144	44	30.12.26	D.	—	+	−	−	−	+	−
145	28	1.1.27	D.	—	−	−	−	+	−	−
146	27	3.1.27	D.	—	+	−	−	−	−	−
147	28	7.1.27	L.	—	+	−	−	−	−	−
148	33	9.1.27	L.	—	+	−	−	−	+	+
149	32	11.1.27	L.	—	+	−	−	−	−	−
150	43	11.1.27	L.	—	−	−	−	+	+	−
151	20	15.1.27	L.	—	−	−	−	+	+	−
152	18	21.1.27	L.	—	−	−	−	+	−	−

TABLE I (*continued*).

No.	Age.	Date of Onset.	Lived or Died.	Complications.	Pn. I.	Pn. II.	Pn. III.	Pn. IV.	Pf.	H. S.
153	21	22.1.27	L.	—	+	−	−	−	−	−
154	25	28.1.27	L.	Slightly delayed resolution; furunculosis	+	−	−	−	+	−
155	31	2.2.27	L.	—	+	−	−	−	−	−
156	24	5.2.27	L.	—	−	−	−	+	+	−
157	40	10.2.27	L.	Empyema	+	−	−	−	−	−
158	45	15.2.27	D.	—	−	−	−	+	−	+
159	38	15.2.27	D.	—	−	−	−	+	−	−
160	35	17.2.27	L.	—	+	−	−	−	−	−
161	27	17.2.27	L.	—	−	−	−	+	+	−
162	17	19.2.27	L.	Empyema	−	−	−	+	−	−
163	19	22.2.27	L.	Furunculosis	−	−	−	+	+	−
164	46	25.2.27	L.	—	−	−	−	+	−	−
165	30	2.3.27	L.	—	−	−	−	+	+	+
166	23	11.3.27	L.	—	+	−	−	−	+	−
167	30	12.3.27	L.	Simple pleural effusion	−	−	−	+	−	−
168	43	18.3.27	D.	—	+	−	−	−	+	−
169	29	21.3.27	L.	Empyema	−	−	−	+	+	−
170	36	22.3.27	L.	—	+	−	−	−	+	−
171	41	23.3.27	L.	—	−	−	−	+	−	−
172	43	1.4.27	D.	—	−	−	−	+	−	−
173	34	3.4.27	D.	—	−	−	−	+	+	−
174	31	4.4.27	L.	—	+	−	−	−	+	−
175	38	8.4.27	D.	—	−	−	−	+	+	−
176	17	14.4.27	L.	—	−	−	−	+	+	+
177	24	14.4.27	L.	Delayed resolution	−	−	−	+	+	−
178	47	20.4.27	L.	—	+	−	−	−	−	+
179	30	20.4.27	L.	—	+	−	−	−	+	−
180	18	26.4.27	D.	—	+	−	−	−	−	+
181	46	1.5.27	L.	—	−	−	−	+	+	−
182	35	1.5.27	L.	—	+	−	−	−	−	−
183	20	7.5.27	L.	—	+	−	−	−	+	−
184	44	15.5.27	D.	—	+	−	−	−	+	−
185	19	19.5.27	L.	—	−	−	−	+	−	−
186	31	19.5.27	L.	Empyema	+	−	−	−	−	+
187	20	19.5.27	D.	—	+	−	−	−	+	−
188	37	22.5.27	D.	—	+	−	−	−	−	−
189	61	29.5.27	L.	—	+	−	−	+	+	−
190	34	31.5.27	L.	—	+	−	−	−	+	−
191	41	8.6.27	D.	—	+	−	−	−	−	−
192	28	16.6.27	L.	—	+	−	−	−	−	−
193	48	19.6.27	L	—	+	−	−	−	−	−

Table II summarizes the preceding table and gives the number admitted during the whole period of the inquiry, viz. January 1925 to June 1927, also the number of deaths and the number showing complications, with their corresponding percentages.

TABLE II.

(Jan. 1925 to June 1927.)

No. of Cases admitted.	No. of Deaths.	No. showing Complications.
193	35	44
—	18·1 %	22·8 %

In 7 out of the 44 cases with complications the patient died.

Table III gives the number of cases from November 1925 to June 1927 and also the types of pneumococci found and their percentages. It will be seen

that from January 1925 to November 1925 no bacteriological examination was carried out.

TABLE III.

(Nov. 1925 to June 1927.)

Type I.	Type II.	Type III.	Type IV.	Total.
50	5	—	61	116
43·1 %	4·3 %	—	52·6 %	—

These two tables are shown graphically in Chart 1, each square representing one case, and the figures in them indicate the type of pneumococcus identified, where such bacteriological examination was made.

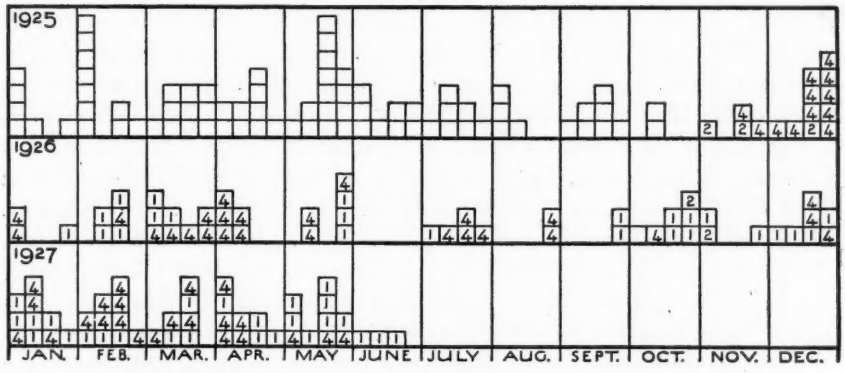


CHART I. Cases of lobar pneumonia admitted to the Manchester Royal Infirmary, Jan. 1925 to June 1927.

In Table IV the figures are given from the Medical Research Council's publication, 1923 (18).

TABLE IV.

Comparison of British and American Results.

	American data (1,632 cases).		British data (361 cases).	
	No. of Cases.	Percentage Incidence.	No. of Cases.	Percentage Incidence.
Type I	532	32·5	138	38·2
,, II	429	26·2	111	30·8
,, III	190	11·6	14	3·9
Group IV	481	29·4	98	27·1
	1,632		361	

In scrutinizing the figures from which Table IV has been constructed, one notes a marked variation in the percentage incidence of the types in the various investigations. For example, Type I varied from 54·8 per cent. (Cole and McCallum, 1918) to 13·8 per cent. (Opie, Blake, Small, and Rivers, 1918). Type II varied from 33·63 per cent. (Dochez and Avery) to 14·9 per cent. (Schorer, Clark, and Sanderson); Type III from 17·8 per cent. (Dickson and Hinton) to no cases (Syndstricker and Sutton). Group IV from 49·4 per cent. (Thomas, 1917–21) to 19·4 per cent. (Cole and McCallum). Cecil, Baldwin, and

Larsen (20) noted in their investigation, which covered a period of five years, that in the various years the incidence of

Type I	varied from	45·2	per cent.	to	21·0	per cent.
Type II	„	„	20·6	„	„	15·9	„
Type III	„	„	17·2	„	„	7·9	„
Group IV	„	„	41·0	„	„	23·5	„

There is thus a fairly well marked variation from year to year and in the different countries in the incidence of the various types.

The points which stand out in our figures are the absence of any Type III cases and the paucity of Type II. The previous statistics show that Type III, rare in Britain, is more than twice as frequent in America in both adults and children. Syndstricker and Sutton, Armstrong and Urquhart do not report any cases of Type III in their investigations. Griffith reports 2·9 per cent. in 67 cases; Glynn, Digby, and Jones, 2·1 per cent. in 96 cases. In no previous investigation have the figures for Type III been so low. Cecil, Baldwin, and Larsen (20), in their recent publication of incidence by type in 1,913 cases of pneumococcal pneumonia, give the following percentages: Type I, 33·6 per cent.; Type II, 19·1 per cent.; Type III, 13·3 per cent,; Group IV, 33·1 per cent. They note that the percentage of Group IV is higher and Type II lower than in the figures of Dochez and Gillespie, and continue: 'The reason for this discrepancy is not clear, but can probably be explained on the basis of a difference in the character of the patients studied in the two series.' On the other hand Sacquépée (21), in the period from April 1919 to March 1921, found in 36 cases of lobar pneumonia 86·0 per cent. of Type II and only 5·5 per cent. of Group IV. Glynn has pointed out the importance of a comparison of the incidence and mortality rates in various countries of the four types of 'pneumococcal' pneumonia, particularly that of Type I.

Differences naturally occur in the figures, some of which are due to recognized factors, such as: (1) Variations in the technique used for the classification of pneumococcal types; this must obviously be an important factor. We have recorded our technique in full, which is largely based on the Rockefeller work. (2) Variations in the age of the patients, to which we shall refer presently. (3) Variations in the type of epidemic; attention has already been drawn to the wide variation in the figures for the percentage incidence of the types from year to year and in different epidemics, although the percentage incidence figures over a considerable period, shown in Table IV, are broadly similar. Our figures for the percentage incidence of Type II and Type III differ widely from many of the preceding figures, and this although the investigation continued over a period of twenty months. (4) Variation in the virulence of the pneumococcus. We believe this to be an important factor. Variations in virulence of the pneumococcus at different periods, under different conditions and at different ages, will probably afford a better explanation of the difficulties encountered in a study of the incidence, mortality, and varieties of pneumonia than is forthcoming from a study of the types. As previously pointed out, R. R. Armstrong and J. F. Gaskell

believe that the virulence of the pneumococcus (without reference to the type) is an important factor in determining whether lobar, broncho-, or 'miliary' pneumonia develops.

The mortality and complication rates are shown in Table V.

TABLE V.

(116 cases from Nov. 1925 to June 1927.)

	Death-rate.		Complication-rate.	
	No. of Deaths.	Percentage.	No. of Complications.	Percentage.
Type I	13	26	11	22
" II	1	20	2	40
" III	0	0	0	0
Group IV	15	24·6	12	19·7
Totals	29	25	25	21·5

The complications included: empyema, simple pleural effusion, delayed resolution, non-resolution, furunculosis, pericarditis, parotitis, peritonitis, endocarditis, phlebitis, abscess, and gangrene of the lung. Empyema was the most frequent complication; it occurred in 13 cases—that is, forming 50 per cent. of the complications and being found in 11·2 per cent. of all cases. This percentage is more than twice as high as that given in a recent American report (20), from which the authors conclude: 'Empyema was the commonest complication, occurring in 5·1 per cent. of cases. Incidence of empyema was considerably higher in Type I infection than in any of the other types.' Of our 13 cases of empyema, 7 belonged to Type I and 6 to Group IV.

The paucity of Type II cases and the absence of Type III make it difficult to compare our figures with those of American workers. The figures at our disposal for the death-rates and complication-rates show a remarkable similarity and do not warrant any conclusion as to any particular type having a higher death or complication rate.

Table VI, which gives the figures for the death-rate, is compiled from the American and British data (18).

TABLE VI.

	American figures (a total of 1,632 cases from 1914 to 1921).		British figures (a total of 361 cases from 1921 to 1923).	
	No. of Deaths.	Percentage.	No. of Deaths.	Percentage.
Type I	43	21·2	23	27·1
" II	42	34·7	19	36·3
" III	46	54·1	1	25·0
Group IV	46	19·1	6	11·5

The general conclusion drawn by the American investigators is that the death-rate from Type II and Type III is almost twice as high as that from Type I and Group IV; at the same time the death-rate from the fixed types is much higher than Group IV. Type III is the most fatal of all types.

Age appears to be such an important factor that we present Table VII,

which shows the relation between the ages and the numbers of deaths and complications in this series of 193 cases.

TABLE VII.

(193 Cases.)

Age Period.	No. of Cases.	Percentage in each Decade.	Deaths. No.	Deaths. Percentage.	Complications. No.	Complications. Percentage.
1-9	6		0		1	
10-19	26 (32)	16·6	1 (1)	3·1	6 (7)	21·9
20-29	56	30·6	6	10·8	14	25·0
30-39	47	24·4	7	15·0	7	15·0
40-49	43	22·3	16	37·2	13	30·2
50-59	9		1		2	
60-69	5 (15)	7·8	3 (5)	33·3	1 (3)	20·0
70-79	1		1		0	

Seventy-six per cent. of the cases occurred between the ages of 20 and 49. The death-rate for the patients under 20 is 3·1 per cent., whereas that for patients over 50 is 33·3 per cent. The death-rate in relation to age shows an increase with advancing age, a fact which is well known. The complication-rate does not present any striking change in the different decades, but from a review of our figures there can be little doubt that age is the most important single factor in determining the death-rate in pneumonia; this is also borne out by the recent American figures.

Table VIII shows the relation of age and type to the mortality and complication rates in 116 cases.

TABLE VIII.

Age Period.	No. of Cases of all Types.	Type I. No. of Cases.	Type I. No. of Deaths.	Type I. No. of Complications.	Type II. No. of Cases.	Type II. No. of Deaths.	Type II. No. of Complications.	Group IV. No. of Cases.	Group IV. No. of Deaths.	Group IV. No. of Complications.
10-19	14	5	1	2	0	0	0	9	0	2
20-29	36	14	2	3	2	0	1	20	3	5
30-39	29	16	1	2	1	0	0	12	5	2
40-49	27	12	8	2	1	1	1	14	4	2
over 50	10	3	1	2	1	0	0	6	3	1
Total No.	116	50	13	11	5	1	2	61	15	12

This shows that the relative occurrence of Type I and Group IV varies very little through the different age periods. In fact only 38·5 per cent. of the cases in the age period 10–19 were Type I, as opposed to 47 per cent. in the age period 40–49.

The American investigators suggest from their figures that: (1) the young are prone to Type I, that (2) the old are prone to Type III, that (3) Type I pneumonia has a low death-rate because it is the pneumonia of the young, and that

(4) Type III has a high death-rate because it is the pneumonia of the old. Also that Type III is not a severe infection under 30, although the death-rate is high in older patients. In the British statistics, although the cases are few, Type III does not show a particularly high mortality-rate. Not a single case of Type III pneumonia was admitted to the Manchester Royal Infirmary under this scheme (although we have found Type III organisms in the throats of normal people); we are thus unable to compare our figures with those of the American writers.

Our figures, however, do not show that the type plays an important part in relation to incidence or mortality, either in a particular age period or in the total figures. They appear to suggest that age is a much more important factor than type in determining the mortality-rate.

In reports dealing with the efficacy of some particular therapeutic procedure, it is not unusual to find comparisons between the death-rate from pneumonia during the period when that procedure was applied, and during a preceding or subsequent period when it was not. The fallacy of such a method of comparison has, of course, been pointed out again and again, and is, indeed, glaringly obvious to any one who has given any thought to the matter. But error dies hard; and when an opportunity arises of presenting a striking illustration of the futility of comparative figures, which are presented without any regard to the first principles of statistics, it may well be accepted. We would, therefore, note the apparently lethal effect of taking specimens of sputum for bacteriological examination. Between January 1, 1925, and October 12 in the same year, 77 cases of pneumonia were admitted to the Manchester Royal Infirmary. Of these 6 died, giving a mortality of 7·79 per cent. During this period specimens of sputum were not taken for bacteriological examination. This procedure was instituted as a routine in November 1925. The first case, whose sputum was examined, died. From then onwards, until the close of the inquiry in June 1927, 116 further cases of pneumonia were admitted. Of these, 29 died, giving a mortality of 25 per cent., more than three times greater than that occurring during the non-bacteriological period. The absurdity of such a conclusion prevents serious consideration; but, had the non-bacteriological period happened to coincide with the application of some particular method of treatment, we strongly suspect that attention would have been drawn in print to the remarkable lowering of mortality for which that method was responsible.

We have examined the mortality and complication rates in a series of 101 cases in relation to the presence in the sputum of a pure culture of pneumococcus or a mixed culture (Pfeiffer's influenza bacillus and haemolytic streptococcus).

TABLE IX.

(101 Cases.)

Culture.	No. of Cases.	No. of Deaths.	Percentage.	No. of Complications.	Percentage.
Pure	46	15	32·6	9	19·6
Mixed	55	11	20·0	8	14·5

In 101 cases, 46 were pure culture and 55 mixed culture; in 44 of the latter Pfeiffer's bacillus was found, in 5 haemolytic streptococcus, and in 6 cases both. In the 101 cases there were 26 deaths, of which 15 were in cases with a pure culture and 11 in cases of a mixed culture. Of the former, 6 were Type I and 9 Group IV; of the latter, 6 were Type I and 5 Group IV. In this series there were also 17 cases with complications, of which 9 were in cases with a pure culture and 8 in cases where a mixed flora was present. Of the 9 pure cultures 6 were Type I and 3 were Group IV; in the 8 mixed cultures 3 were Type I and 5 were Group IV. In the 46 cases of pure culture 22 were Type I, 1 Type II, and 23 Group IV. In the 55 cases of mixed culture 28 were Type I, 1 Type II, and 26 Group IV.

The figures are small, but there is not any apparent relation between the presence of a mixed flora and the pneumococcus type. The mortality and complication rates were higher in those cases with a pure culture.

During the course of the examination of our records we looked for any evidence of any correlating feature between the type on the one hand, and on the other, sex, occupation, mode of onset, presence of herpes, rigor, particular lobe involvement, number of lobes involved, the duration of the disease, and mode of termination.

We found no correlating feature, and we were unable to note any difference clinically between pneumonia cases of the various types. We are unable to support the view expressed that herpes or rigor is more frequent in Type I.

TABLE X.

	Cases reported as		Deaths from	
	Primary Pneumonia.	Influenzal Pneumonia.	Primary Pneumonia.	Influenzal Pneumonia.
1925.				
July	157	6	49	3
*August	98	3	43	4
September	123	5	36	7
*October	180	16	61	8
November	248	19	84	15
December	280	34	125	14
1926.				
*January	165	17	69	17
February	211	31	94	13
March	225	39	89	44
April	180	57	90	43
*May	132	25	50	21
June	122	13	57	13
*July	89	8	47	5
August	49	10	21	3
September	56	4	30	3
*October	148	15	44	8
November	289	30	94	20
December	240	26	71	9
1927.				
*January	198	28	77	29
February	312	194	141	143
March	291	189	169	163
*April	160	35	52	32
May	185	23	64	10
June	187	16	63	6

* = Figures for four-fifths of a month of 5 weeks.

Pneumonia Incidence and Carrier Rate in Manchester.

We are permitted to include a table showing the monthly incidence of pneumonia and what is designated as influenzal pneumonia in Manchester during the period July 1925–June 1927. This table (Table X) also includes the death-rate from each condition, and the whole is shown graphically in Chart II. The seasonal variation is well indicated, but particular attention is drawn to the rise in influenza during the winter of 1926–7 compared with the winter of 1925–6. Both winters are marked by the incidence and mortality of primary pneumonia.

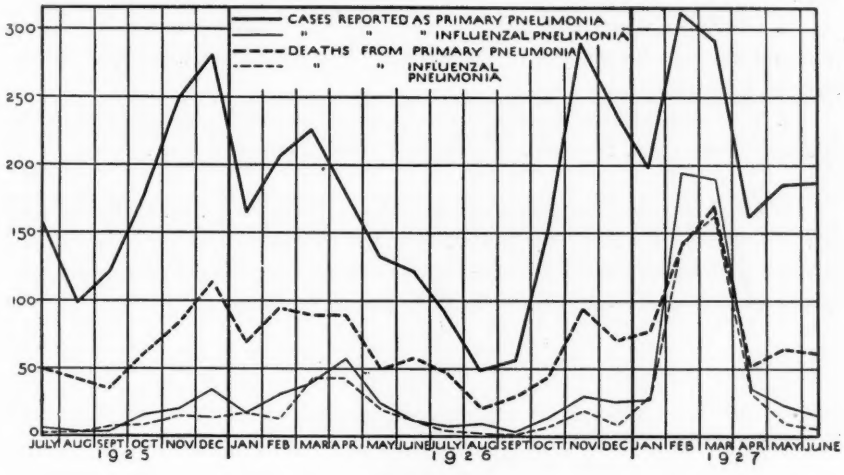


CHART II.

Summary.

The full clinical data of 193 cases of primary lobar pneumonia during a period of two and a half years, extending from January 1925 to June 1927, are given. The type of pneumococcus present in the sputum is recorded in 116 cases, occurring in the period from November 1925 to June 1927; and in 101 of these cases the presence or absence of Pfeiffer's influenza bacillus and the haemolytic streptococcus is noted.

The pneumonia situation is shortly reviewed, especially in connexion with its varieties, types and mortality. The methods employed in the bacteriological examination are reported; the results of the investigation and the factors of type, age, mortality, and complications are tabulated and compared with other British and American statistics.

Charts are included showing the variations in the bacterial flora of the naso-pharynx of a sample of the population of Manchester from July 1925 to June 1927, and during this period, also, the cases reported and the death-rate from primary pneumonia and influenzal pneumonia.

Conclusions.

1. There is considerable variation in the percentage incidence of types of pneumonia from year to year and in different countries.

2. Type III is much less common in this country than in America.

3. There is not any relation between the types of pneumococcus found in the sputum and the mortality or complication rates.

4. Probably the most important factor in prognosis is age.

5. There is not any relation between the clinical picture, the mode of onset, the course, the severity, the mode of termination, and the causative type.

6. There is not any striking relation between the presence of a mixed infection and the severity or type of pneumonia. The death-rate was higher in our cases of pure infection.

7. It would be more practicable and useful to classify pneumonias on a bacteriological rather than on a clinical or morbid anatomical basis.

We wish to record our debt of gratitude to Professor W. W. C. Topley and to thank him for his many kindnesses. We also wish to express our indebtedness to the physicians of the Manchester Royal Infirmary for permission to use their cases and to the house-physicians for their very ready help.

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THE OSMOTIC PRESSURE OF THE BLOOD PROTEINS IN NEPHRITIS[1]

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The well-known principles enunciated by Starling in 1896 (16) to explain the phenomena of lymph formation have as yet failed to afford such a simple explanation of the oedema found in various clinical conditions as they appeared to promise. Consideration of the mass of experimental data collected since that time tends to show that factors other than those physico-chemical ones involved in the mechanism described by Starling are concerned, at least in some types of oedema.

The factors most clearly involved may be divided into two main groups: (1) The extra-capillary factors, namely, those which lead to retention of water in the tissues: (*a*) 'Quellung', or the swelling pressure of proteins; (*b*) primary tissue salt retention; (*c*) lymphatic obstruction. (2) The intra-capillary factors, namely, those which cause increasing transudation and lymph production: (*a*) raised capillary pressure; (*b*) increased capillary permeability; (*c*) lowered protein osmotic pressure of the blood plasma.

The influences of the latter group (2), which comprise those concerned in the mechanism described by Starling, are to a large extent interdependent and have been analysed as regards their role in transudate formation by Landis (8) in the tissues of the frog. But the precise extent to which they are concerned in oedema formation in the human subject has never been fully determined, owing to the extreme difficulty of procuring reliable measurements of the capillary blood-pressure in the oedematous tissues concerned, to the even greater difficulty of obtaining any index of capillary permeability changes in such areas, and, in the past, to the technical difficulties encountered in measuring the protein osmotic pressure of plasma on the relatively small samples which can conveniently be obtained from the human. This last factor differs from the others in being the only one which does not vary rapidly from time to time and from region to region of the body, so that it is capable of direct measurement in the blood drawn from any part of the general circulation. In recent years the ingenuity of Govaerts (5) has designed a simple yet practical osmometer that has almost completely overcome the technical difficulties of measuring osmotic pressure,

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although the method is still somewhat too laborious for general clinical application.

In the present work the technique described by Verney (17), who has modified that of Govaerts in detail, has been employed in an endeavour to determine the extent to which protein osmotic pressure change in the blood plasma can be invoked as an explanation more particularly of renal oedema, since this type more than any other appears to defy explanation in terms of the Starling mechanism. Observation on man rather than on animals is necessitated by our inability to reproduce in animals a condition of oedema which can justifiably be compared with that encountered in man suffering from nephritis.

Method.

Blood samples were taken from an antecubital vein into a sterile syringe, the minimum time of blood stasis being permitted in the limb, since it is known that the prolonged application of a tourniquet alters to an appreciable extent the concentration of blood-plasma proteins in the limb (13).

The blood, usually 10 c.c., was oxalated with three drops of a saturated solution of potassium oxalate, and the plasma centrifugalized off in sterile tubes under paraffin. The plasma so obtained was used to charge the osmometers according to the method of which the details have been described by Verney, and which need not, therefore, be further described here. As semi-permeable membrane, 'cellophane' substance No. 253 was used, this material meeting all requirements as regards impermeability to proteins and ease of sterilization without serious change in properties.

Osmometers were set up in triplicate, or in duplicate if the amount of plasma were inadequate, and allowed to remain at constant temperature (20° C.) for 36–48 hours. As a rule, constancy of readings was attained in 24 hours, and those osmometers which failed to reach equilibrium, and showed either an excessive tendency to rise, indicating infection with organisms, or to fall, indicating probable leakage, were discarded as unreliable.

Protein and non-protein nitrogen estimations were made on plasma samples both before and after dialysis, and in some cases a non-globulin nitrogen estimation was also performed in order to obtain a value for the albumin-globulin ratio. All nitrogen estimations were carried out in a micro-Kjeldahl apparatus using N/70 acid and alkali, and were duplicated. In such investigations a chemical method is undoubtedly preferable to a purely physical one, such as the refractometric or the visco-refractometric, owing to the complete freedom of the former from any complications arising from variations in composition and properties of the plasma used.

A small but definite alteration in protein concentration in the osmometer, usually a dilution, not infrequently occurs during the process of dialysis. To allow for this the osmotic pressures given are theoretical values calculated from the observed pressure per gramme of protein in the osmometer, and adjusted to

the basis of the observed protein concentration in the plasma before dialysis. Thus: Osmometer readings: 29·2 and 28·6 cm. of water. Average is 28·9.

Total nitrogen (dialysed plasma) 946 mg. per cent. c.c.

Total nitrogen (undialysed plasma) 1,050 mg. per cent. c.c.

Hence the derived osmometer reading is 32·0 cm. of water.

Clinical Material.

The cases examined have been grouped under the following heads: (1) Healthy normals. (2) General non-nephritic cases without oedema. (3) General nephritic cases without oedema. (4) Cardiac cases with oedema. (5) Nephritic cases with oedema.

Measurement of the degree of oedema is difficult and has been arbitrarily made as follows: ? ± slight oedema. + definite slight oedema. + + moderate oedema. + + + severe oedema. + + + + severe oedema with ascites and/or effusion.

An effort was made to decide the group in which each case should be placed before the osmometer measurement was made, in order as far as possible to eliminate bias, but no claim is made that such a scale is more than a rough clinical impression of the degree of oedema.

TABLE A. *General Non-nephritic Cases without Oedema.*

No. in Series.	Initials.	Age.	Oedema.	Osmotic Pressure cm. H_2O.	Protein Nitrogen mg. % c.c.	Osmotic Pressure per grm. Protein.	Non-protein Nitrogen mg. % c.c.	Remarks.
1	K. E. H.	26	–	32·0	963	5·33	34·5	Normal subject.
2	C. L. C.	25	–	32·0	1050	4·89	69	,, ,,
3	A. Cons.	52	–	31·3	1065	4·70	60	Gastric ulcer. Thin, but not wasted.
4	G. H.	46	–	30·9	1080	4·68	48	Osteo-arthritis.
5	G. Hill	52	–	44·1	1014	5·96	46	Polycythaemia rubra, 15.3.27. R.B.C. 7,650,000.
6	,,	52	–	39·9	958	6·66	50	Polycythaemia rubra, 9.5.27. R.B.C. 5,900,000.
7	A. C.	43	–	19·8	860	3·68	50	Polycythaemia rubra, 10.2.27. R.B.C. 6,000,000. Hb. 84 %.
8	,,	43	–	24·8	790	4·92	30	Same case after phenylhydrazine, 1.4.27. R.B.C. 3,900,000.
9	J. H.	43	–	26·7	947	4·52	141	Osteo-sclerotic anaemia. Carc. prostate.
10	Thom.	24	–	28·3	912	4·97	44	Anaemia from carcinoma.
10a	D. R.	45	–	27·7	1124	3·96	48	Myocardial failure. No oedema.
				General Non-nephritic Cases with Oedema.				
11	R. C.	42	+ + + +	20·2	855	3·77	71	Hepatic cirrhosis, ascites, and oedema.
12	G. R.	20	+	48·0	1064	7·21	40	Chronic oedema of Milroy type.

In this series (Table A) the plasma protein osmotic pressure in healthy normal individuals is between 30 and 32 cm. of water, but in those cases suffering from general diseases not causing oedema the variation in osmotic pressure is considerable. The low values encountered in A. C. (Nos. 7, 8) on two occasions were unassociated with any but the slightest tendency to oedema formation, a slight oedema of the ankles in the evening being attributed to coincident varicose veins. The variations encountered are wider than the limits given by Govaerts (5, 6) for general disease states, and do not entirely bear out

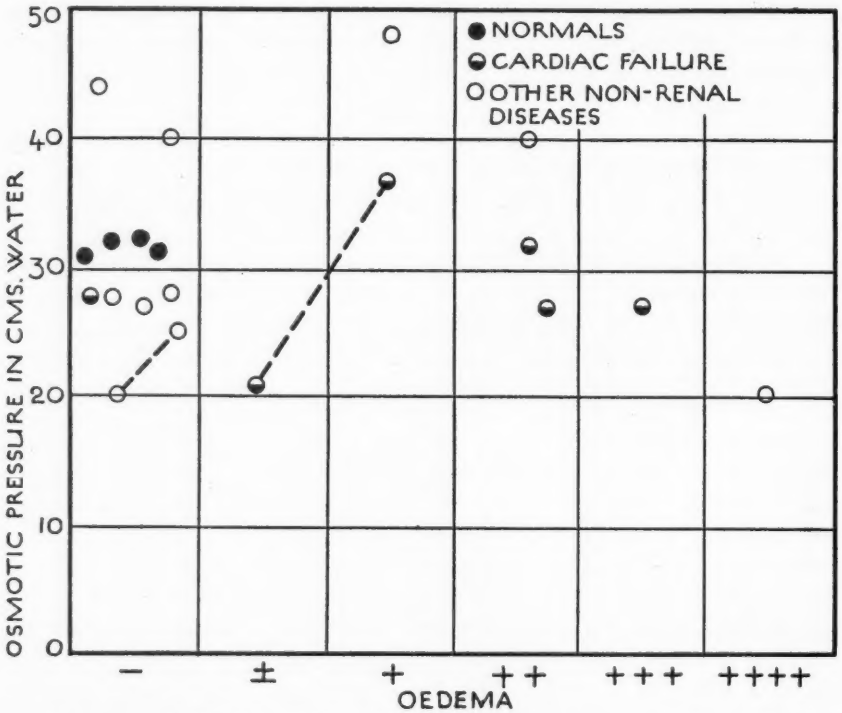


FIG. 1. Illustrating the variability of blood protein osmotic pressure in non-oedematous patients with normal kidneys and the relatively undepressed valves in cardiac oedema. Broken lines joining points indicate successive observations on the same case.

his statement that absence of oedema is associated with the maintenance of osmotic pressure above 30 cm. of water. Whilst an increased protein concentration is so unusual as to provoke comment, some decrease is frequently encountered in disease, and with this fall there tends to be a fall in osmotic pressure values. If this fall continue sufficiently it may possibly lead to such an oedema state as is encountered in famine and similar cachexias, but osmotic pressures between 25 and 30 cm. of water are quite compatible with freedom from oedema. The same deductions must be made from the well-known experimental fact that dilution of the plasma to a considerable degree by saline infusion after bleeding does not ordinarily lead to oedema formation.

On the remaining two cases with oedema, little comment is necessary. R. C. (No. 11) had the low plasma protein value which is frequently encountered in hepatic disease and a correspondingly low osmotic pressure, a value which no doubt greatly favours the transudation of fluid as a result of the raised venous pressure in the portal and inferior vena caval systems.

G. R. (No. 12) was a healthy young girl with persistent oedema of the ankles of Milroy's type, but differing from this in the absence of any hereditary element. A tentative clinical diagnosis of 'chilblain' circulation was given. This being so evidently a local condition, no depression of the protein osmotic pressure would be expected. Possibly the rise in value is compensatory.

TABLE B. *Nephritic Cases without Oedema.*

No. in Series.	Initials.	Age.	Oedema.	Osmotic Pressure cm. H_2O.	Protein Nitrogen mg. % c.c.	Osmotic Pressure per grm. Protein.	Non-protein Nitrogen mg. % c.c.	Blood-pressure.	Remarks.
13	A. F.	5	–	42·9	1156	6·09	34·5		Post-scarlatinal albuminuria.
14	D. M.		–	46·9	1089	6·80	37·5	110	? Acute nephritis.
15	E. A.	22	–	48·0	1231	6·11	77	110	Acute nephritis 6 weeks before.
16	M. W.		±	30·9	1072	4·61	202	130	Uraemia.
17	A. Sch.	26	–	47·9	1240	6·18	165	120	Uraemia, chronic.
18	Cw.	48	–	34·3	1114	4·90	66	200	Chronic nephritis. Hypertension.
19	Edel.	29	±	27·0	1000	4·32	49	190	Uraemia, chronic.
20	„	29	±	31·0	923	5·37	195	200	Do. later, one week before death.
21	J. P.	36	–	31·5	965	5·23	89	220	Uraemia, chronic.
22	„	36	–	30·5	1018	4·80	178	160	Do. later.
23	„	36	±	27·3	951	4·58	120	150	Do. later, one week before death.
24	G. McG.	43	–	28·5	1024	4·46	66	135	Acute nephritis at recovery.
25	F. L.	35	–	31·0	1170	4·78	74	110	Acute nephritis at recovery.
26	E. K.	48	–	31·4	895	5·61	40	130	Acute nephritis during recovery.
27	„	48	–	33·2	1163	4·57	50	140	Do. 10 days later.

The marked tendency to maintenance of the normal protein osmotic pressure with but slight depression in this series (Table B) is evident; what little reduction there is may probably be accounted for by the condition of general debility. The reason for the high values encountered in four of these cases is not clear.

D. M. (No. 14) had oliguria, pain in the loin, and blood in the urine. No tubercle bacilli were ever detected. Clinical diagnosis, 'haemorrhagic nephritis'.

A. F. (No. 13) was a child of five years with albuminuria three weeks after scarlet fever. There was no oedema. The osmometric reading was in this case based on a single observation.

A. Sch. (No. 17), a girl of 26 years, had a history of recurrent attacks of nephritis over a period of ten years, commencing as acute parenchymatous nephritis after scarlet fever. At the time of examination her urine contained albumin + +, but no blood. Blood-pressure 120, though it had been higher in

the past, and blood urea 180 mg. per cent. c.c. Ocular fundi normal. Uraemic symptoms slight, although she had had a positive diazo reaction for over a year. Probably a contracted kidney. It is of interest that, although this girl had had albuminuria for six years, averaging 1 per cent. to 2 per cent., and had been on a restricted protein diet, yet she contrived to maintain a high blood protein content.

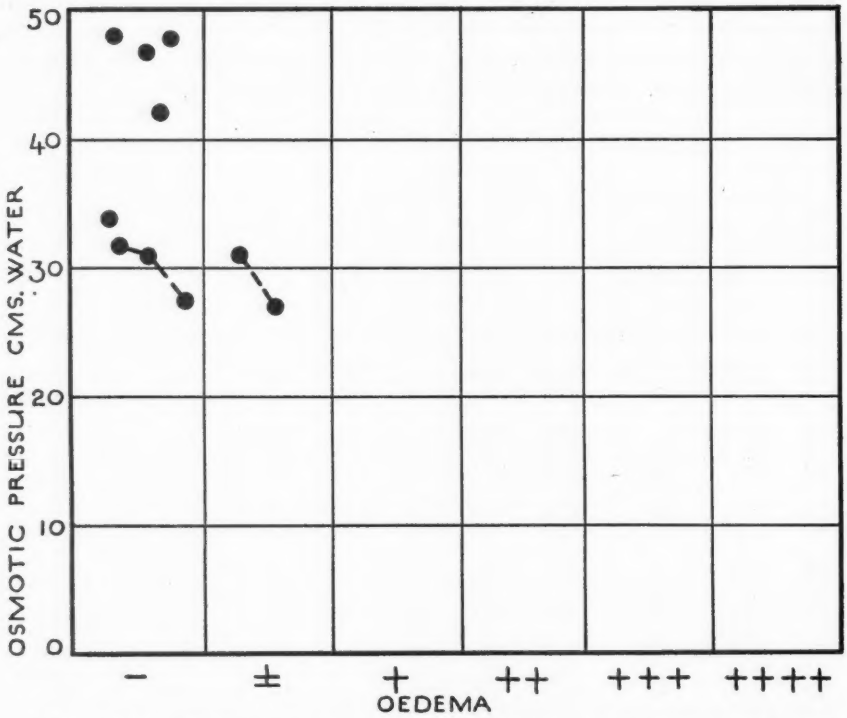


FIG. 2. The blood-plasma protein osmotic pressures in azotemic and other non-oedematous nephritis, showing no depression.

E. A. (No. 15). Aged 22. History of acute nephritis one month ago, with oedema. When the examination was made his blood urea was normal. No albuminuria, but a few red cells and epithelial casts. In the recovery stage.

The absence of any serious reduction in the normal osmotic pressure of these cases is in agreement with the findings of Govaerts and of Mayrs (11). The former observer in his group of cases of 'glomerulo-nephritis without oedema' obtained figures varying from 29 cm. to 35 cm. of water, whilst the latter observed only a moderate reduction in his cases of 'azotemic nephritis'. Special attention may be called to the last three examples in the series B. In both G. McG. (No. 24) and in F. L. (No. 25) recovery was associated with a very definite rise in protein concentration as well as in osmotic pressure. In E. K. (Nos. 26, 27) the former occurred without the latter, or rather the osmotic pressure rose before

protein concentration. Such an observation, if it can be extended to other cases, may possibly help to explain the present apparently hopeless discrepancies between protein concentration and oedema, such as were found for instance by Fahr and Swanson (4).

	Oedematous Stage.			Non-oedematous Stage.					
	No.	Osmotic Pressure.	Protein Nitrogen.	No.	Osmotic Pressure.	Protein Nitrogen.	No.	Osmotic Pressure.	Protein Nitrogen.
F. L.	38	24·3	885	25	31·0	1170			
					5 days later.				
G.McG.	39	17·7	706				24	28·5	1024
								3 weeks later.	
E. K.	40	23·1	880	26	31·4	895	27	33·2	1163
					5 days later.			3 weeks later.	

The great variability of the 'unit' osmotic pressure, by which is meant the osmotic pressure calculated from the actual observations as being exerted by 1 gramme of protein in 100 c.c. of solution, shows that no deduction can be made from simple protein concentration determinations as to changes in the osmotic pressure exerted by the protein. Thus in one case examined, but excluded from all groups owing to the obscurity of diagnosis, a normal total protein content of the blood was associated with a low osmotic pressure, and only later did the protein concentration fall.

	No.	Osmotic Pressure.	'Unit' O. P.	A/G.	Protein Nitrogen.	Oedema.	Date.
S. J.	47	24·0	3·43	0·316	1120	+ +	30.1.28
„	48	23·0	3·80	0·60	975	+ +	21.2.28

This man had cardiac valvular disease, persistent temperature, much oedema of legs, sacrum, and scrotum (+ +). Occasional attacks of haematuria. Negative blood culture. Whether the oedema was of cardiac or renal origin was undecided.

Now Govaerts (6) claims that the 'unit' osmotic pressure is dependent on the albumin/globulin ratio of the plasma protein concerned. On plotting observed 'unit' osmotic pressure against A/G ratio the points obtained by him tend to fall on a curve which can be obtained theoretically by ascribing to albumin and globulin respective 'unit' osmotic pressures of 7·54 and 1·95 cm. of water. A similar conclusion was reached by von Farkas (3), who, however, ascribes different 'unit' osmotic pressures to the albumin and globulin fractions (i. e. 6·8 and 2·5 cm. of water respectively). See Fig. 4.

The values obtained in the present investigation do undoubtedly fall on a similar curve, although uniformly below those of both Govaerts and von Farkas. The difference in absolute values is probably one of technique, as is pointed out later. If, then, such a relation does indeed exist it will be possible, as Govaerts points out, to predict the osmotic pressure from a fractional analysis of the plasma protein into its albumin and globulin portions.

No clear relation between blood-pressure and osmotic pressure is to be made out from these figures. High protein osmotic pressure readings were associated with normal blood-pressure and normal osmotic pressures with hypertension.

TABLE C. *Cases of Nephritis with Definite Oedema.*

No. in Series.	Initials.	Age.	Oedema.	Osmotic Pressure cm. H_2O.	Protein Nitrogen mg. % c.c.	'Unit' Osmotic Pressure per grm. Protein.	Non-protein Nitrogen mg. % c.c.	Blood-pressure. mm. Hg.	Remarks.
					Nephrosis Type.				
28	J. S.	22	+ + +	11·3	749·6	2·42	30·4	95	7.3.27. Pure nephrosis.
29	„	22	+ + +	8·0	675	1·92	34·0	95	27.4.27. Urine: a few blood cells and epithelial and granular casts. Urea concentration test 1·7 %. Oedema persisted over 12 months.
30	J. D.	57	+ + + +	14·5	700	3·30	102	190	Of nephrotic type, but with high blood urea and blood-pressure. Between the second and third determinations her ascites had been tapped, but oedema remained practically constant throughout.
31	„	57	+ + + +	15·4	750	3·28	80·8	190	
32	„	57	+ + + +	16·2	720	3·52	120·0	170	
					Glomerulo-nephritis.				
33	G. B.	19	+ +	26·3	888	4·74	56·5	170	Subacute nephritis of 8 days' duration. Urine 0·5 %–1 % of albumin. Granular, epithelial, and hyaline casts and red blood cells. Arteries tortuous and thickened.
34	A. S.	39	+ +	24·1	752	5·13	40	105	Subacute nephritis. Two previous acute attacks. Post mortem, no evidence of chronic lesion.
35	R. B.	32	+ + +	19·7	847	3·72	55·5	114	Large white kidney at post-mortem.
36	A. H.	11	+ +	28·2	1030	4·37	93	130	Acute nephritis. 14 days' history, commencing with haematuria.
37	E. B.	39	+ + +	23·6	770	4·91	190	160	Subacute nephritis with uraemia. Blood urea 300. Haematuria at onset 10 days before.
38	F. L.	35	+ +	24·3	885	4·39	53·0	140	Acute nephritis. Oedematous stage. 5th day after acute onset. Urine: albumin and blood + +.
39	G. McG.	43	+ +	17·7	706	4·02	44·0	130	Acute nephritis. Oedematous stage of less than 1 week's duration. Urine: albumin and blood +.
40	E. K.	48	+ +	23·1	880	4·20	70·0	124	Subacute nephritis with oedema, 14 days' duration. Urine: albumin and blood +.

It has been claimed by Govaerts that in cases of essential or primary hypertension the osmotic pressure is found to be high. Such cases have not, however, been included in the present series.

Considerable difficulty is encountered in classing many cases as definitely renal oedemas, especially when these tend to be atypical, and several have had to be discarded because of this uncertainty. Of the series in Table C there was, however, no doubt.

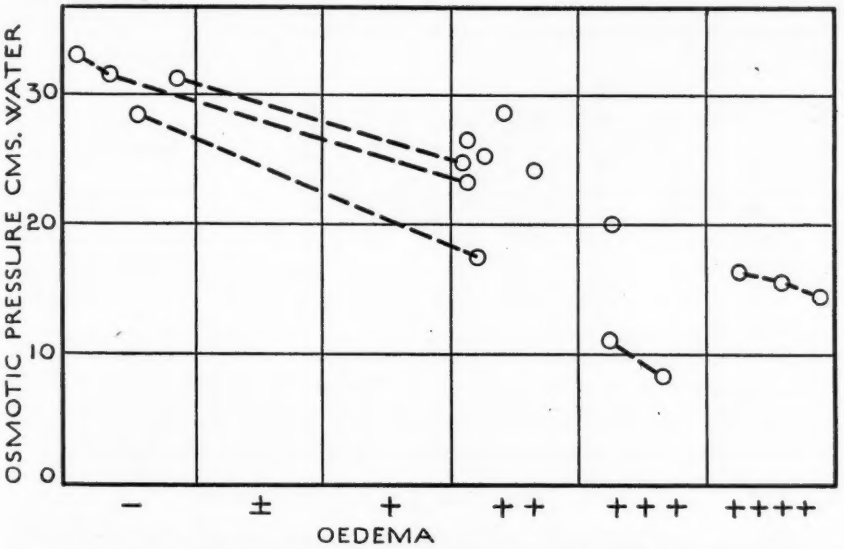


FIG. 3. Showing the depression of protein osmotic pressure in nephritis with oedema and its rise with subsidence of the oedema. Broken lines joining points indicate successive observations on the same case. See Table C.

Many observations have now shown that the approach to a clinical picture of nephrotic type is associated with profound diminution of the osmotic pressure of circulating proteins, a fact first called attention to by Krogh (7) in a case examined by him. J. S. (Nos. 28, 29) was a pure nephrosis with much generalized oedema, no haematuria, normal blood urea, low blood-pressure, and milky plasma (blood cholesterol not determined). In her the low osmotic pressure is associated with a low plasma protein concentration and great depression of the 'unit osmotic pressure', but the albumin/globulin ratio was unfortunately not determined. In J. D. (Nos. 30, 31, 32), however, who departed from the characteristic nephrotic picture only in having high blood-pressure and blood urea, the A/G ratio (see Table D) had fallen to 0·58 coincident with fall in 'unit' osmotic pressure from normal of about 4·65 to 3·52.

The eight cases of glomerulo-nephritis have been chosen as showing the greatest amount of 'hydraemic' type of nephritis, i.e. of oedema and albuminuria, with the minimum of 'azotemic' change, as shown by rise of blood-pressure and nitrogen retention. Since a continuously graded series of types

would appear to exist, ranging from a purely 'hydraemic' on the one hand to a purely 'azotemic' on the other, any absolute demarcation is impossible. There can be no doubt, however, that in cases in which the odematous factor is predominant, a very definite lowering of the osmotic pressure has occurred, and with it a lowering of the 'unit' osmotic pressure. It has been known for some time that dilution of the blood proteins occurs in these cases.

Evidence exists which tends to show that the mechanism involved in the production of cardiac oedema is different from that concerned in renal oedema. Three cases of purely cardiac origin have been investigated:

No. in Series.	Initials.	Oedema.	Osmotic Pressure cm. H_2O.	Protein Nitrogen mg. % c.c.	'Unit' Osmotic Pressure per grm. Protein.	Non-protein Nitrogen mg. % c.c.	Blood-pressure.	Remarks.
41	M. D.	+ + +	27·0	1055	4·58	50	120	Severe oedema. Valvular disease. Aged 62.
42	J. D.	+ +	26·4	998	4·23	80	126	Myocardial failure. Aged 37.
43	E. G.	+ +	31·8	1032	4·90	26	168	„ „ Aged 71.

These illustrate the relatively smaller reduction in osmotic pressure in such cases. Similar findings have been made by Govaerts for osmotic pressure, whilst the relatively slight dilution of proteins has been reported by many, and notably by Rowe (1917) (14). Sometimes an obviously mixed picture is obtained:

44	E. M.	+ +	39·9	1330	4·80	75	200	Aged 80.

This patient had very marked arteriosclerotic changes in her vessels, frequency of micturition eight months, haemorrhagic exudate and tortuous vessels in the fundi, high blood-pressure, and a little albumin in the urine. She clearly had an arteriosclerotic kidney, and upon this was superimposed an oedema due to myocardial failure. A similar case was:

45	H. J.	+	36·3	1114	5·28	80	175

At the time of the measurement on 5.12.27 there was only slight oedema, due to cardiac failure associated with emphysema. Arteriosclerosis was severe in this man also, and there were retinitis and slight albuminuria. Some months after the first determination he developed both ascites and pleural effusion with a fair amount of oedema. These were tapped and, together with the oedema, subsided. Shortly afterwards, on 6.3.28, a second measurement (No. 46) was made. Its value was in large measure destroyed by the fact that during the effusion stage he had been venesected some 20 oz. on 24.2.28.

46	H. J.	±	20·2	780	3·86	50	200

Whether or not this low value is due to the venesection does not matter for the present consideration. The low osmotic pressure must have favoured the production of the ascitic and pleural transudates, but that it can persist after

the oedematous stage has passed off would appear to be significant. The osmotic pressure is lower than was encountered in all but one of the pure nephritic oedema cases and yet was at the time of determination unassociated with any but the slightest suggestion of oedema. (See Fig. 1.)

The chaotic state of the classification of types of nephritis, and the possible close association of a cardiac element in the oedema produced in some of these cases renders interpretation of the results difficult.

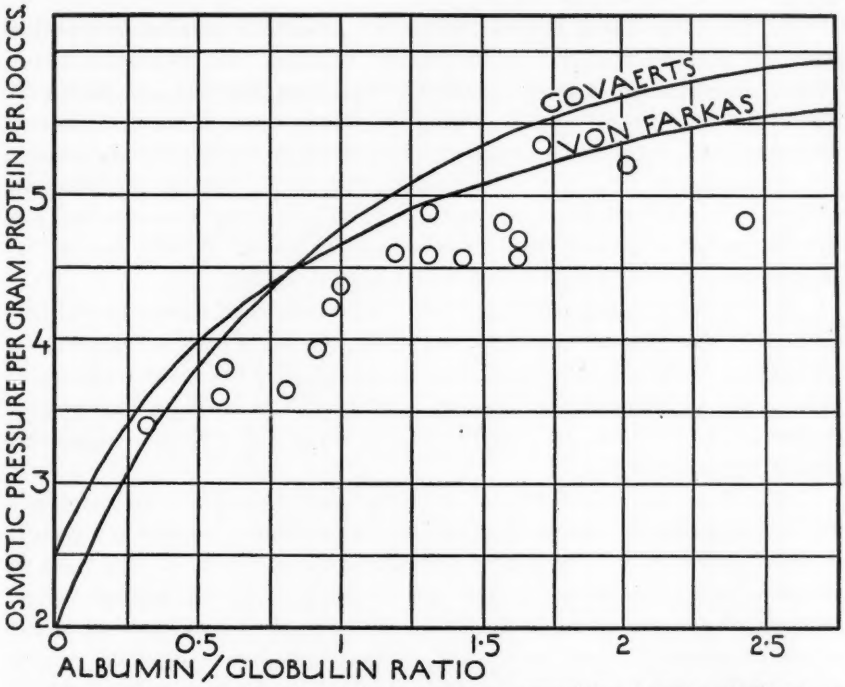


Fig. 4. Curves showing the relation of protein composition, in ratio of albumin to globulin, to the unit osmotic pressure exercised by the protein. Each circle refers to a separate observation detailed in Table D.

It would seem, however, that the following generalizations can be made:

1. The normal blood-plasma protein osmotic pressure, measured by this method, lies between 30 cm. and 32 cm. Such figures agree well with those obtained by Verney (17), using the same technique, and with those of Marrack and Hewitt (10), who employed collodion membranes for dialysis. They are, however, distinctly lower than the values obtained by Govaerts, especially in his later work (6), and than the values obtained by Mayrs (11) in mixed normal serum. Schade and Claussen (15), measuring the 'onkotic pressure', also obtained figures lower than those of Govaerts, so that it would seem that the actual absolute figure obtained depends to a certain extent upon the method employed in a particular case. No great importance is, therefore, attached to absolute values in the present instance, although the constancy of the values

obtained in successive determinations on the same subject indicates that one is justified in using the method to measure changes in the osmotic pressure.

2. The osmotic pressure in cases of chronic interstitial and other forms of non-oedematous nephritis is only slightly reduced, and no more than may be encountered in other types of general disease. Such a conclusion is in complete agreement with the findings of Govaerts and with the known behaviour of the plasma proteins under these conditions, as determined by such observers as Epstein (1912) (2) and Rowe (1917) (14).

3. There is a definite reduction of osmotic pressure in oedematous nephritis and this tends to disappear as the oedema subsides. The depression of the protein concentration in renal oedema has often been described, and Krogh (7) first observed a lowered protein osmotic pressure in a case of renal oedema, an observation which has been confirmed and considerably extended by Govaerts.

Nonnenbruch (12) did, however, in 1921, report three cases in which oedema of apparently renal origin was associated with a high protein concentration, but this observation does not appear to have been confirmed. In only two of the present series was the protein concentration normal or high.

A. H. (No. 36) was a child, aged 11, with fourteen days' history of nephritis with severe and generalized oedema, and in him the fall in protein concentration was slight. E. M. (No. 44), the other case, was nephritic with associated cardiac oedema, and is comparable to those of Nonnenbruch in having a high protein content associated with considerable oedema, but in this case the oedema was plainly of cardiac origin.

4. In those cases of oedema due to parenchymatous nephritis and nephrosis no clear indication of a parallelism has been demonstrated between the protein osmotic pressure and the degree of oedema. A similar lack of parallelism is shown in the observations of Fahr and Swanson (1926) (4), and of Linder, Lundsgaard, and van Slyke (9) upon the relation of the plasma proteins to the degree of oedema. There is, however, no direct relation between the protein concentration and its osmotic pressure. As has already been pointed out, in three of the present series there has been demonstrated a definite return of the osmotic pressure to near its normal value within a short space of time, and coincident with disappearance of the oedema. To such an extent parallelism can be demonstrated, and in this respect oedema of renal origin differs from that of cardiac.

5. In cases of the nephrotic type and in pure nephrosis the fall in osmotic pressure is extreme, as also is that of the protein concentration. This has been observed constantly in pure nephrosis and can no longer be doubted. Pure nephrosis is a relatively rare condition, however, although the occurrence of a similar picture complicating more definitely nephritic manifestations is extremely common.

6. The plasma protein osmotic pressure in oedema from myocardial failure is only slightly reduced and is markedly higher than in cases presenting a similar degree of oedema of renal origin.

As long ago as 1904 Brandenstein (1) had pointed out that no reduction in the protein concentration occurred in even severe cardiac oedema. This fact was confirmed by Rowe (14), using much more accurate methods, in 1917, and was extended to include osmotic pressure by Govaerts, although this author claims that some dilution does occur in valvular disease with oedema.

(7) Coincident with the fall in osmotic pressure there is usually a depression of the 'unit' osmotic pressure, i.e. the pressure exerted by 1 grm. of protein in 100 c.c. of solution.

Verney (17) has shown that dilution of a normal plasma with saline causes a reduction in the 'unit' osmotic pressure. The main factor concerned, however, is probably an alteration in the albumin/globulin ratio. In some of the cases examined the A/G ratio was determined, and a relation between this and the 'unit' osmotic pressure is demonstrable, as has indeed been shown by both Govaerts (6) and von Farkas (3).

TABLE D. *Details of Observations plotted in Fig. 4.*

No. in Series.	Initials.	Osmotic Pressure cm. H_2O.	'Unit' Osmotic Pressure per grm. Protein.	Albumin N.	Globulin N.	Total Protein Nitrogen.	A/G Ratio.	Oedema.	Remarks.
4	G. H.	30·9	4·68	658	406	1080	1·62	−	Osteo-arthritis.
9	J. H.	26·7	4·52	536	411	947	1·30	−	Osteosclerotic anaemia.
10	Thom.	28·3	4·97	646	266	912	2·43	−	Anaemia due to malignant disease.
10a	D. R.	27·7	3·96	540	583	1124	0·93	−	Cardiac failure.
16	M. W.	30·9	4·61	589	493	1072	1·20	−	Uraemia.
20	Edel.	31·0	5·37	583	340	924	1·72	±	Chronic uraemia.
21	J. Peng.	31·5	5·23	645	320	967	2·01	−	Chronic uraemia.
22	„	30·5	4·80	622	396	1018	1·57	−	Chronic uraemia.
23	„	27·5	4·59	589	362	951	1·63	±	Chronic uraemia.
32	J. Dick.	16·2	3·52	264	456	720	0·58	+ + + +	Glomerulo-tubal nephritis.
36	A. H.	28·6	4·37	524	522	1046	1·00	+ +	Subacute nephritis.
42	J. Dixon	26·3	4·23	482	516	998	0·93	+ +	Myocardiac oedema.
43	E. G.	31·8	4·9	588	444	1032	1·32	+ +	Myocardial failure.
47	S. J.	24·0	3·43	269	851	1120	0·316	+ +	? Inf. endocard. with heart failure, 30.1.28.
48	„	23·0	3·80	366	608	975	0·603	+ +	21.2.28.
49	L. W.	17·5	3·65	377	467	854	0·81	+ + +	Pregnancy kidney. Oedema now mostly subsided in bed.
53	J. Cast.	22·1	4·53	459	321	780	1·435	+	Subacute and interstitial nephritis. Recent oedema subsiding. Uraemic symptoms. N.P. Nit. 38 mg. % c.c.

The points plotted lie on a curve definitely below those of Govaerts and of von Farkas (Fig. 4), and the 'unit' osmotic pressure is about 0·5 cm. per gramme of protein below the value of Govaerts for any given A/G ratio. It must be concluded, therefore, that the technique here employed gives osmotic pressure values consistently from 2 to 3 cm. below those of Govaerts, and in com-

paring results allowance must be made for this fact. In this way can be explained the low osmotic pressure values for normal subjects.

The question whether or not osmotic pressure can be invoked as an explanation of nephritic oedema cannot be answered from the data as they at present exist. There is still no evidence that the oedema of nephritic disease is primarily of renal origin. There is indeed a considerable body of opinion leaning towards the view that in hydraemic nephritis there is an associated general metabolic disorder, and this is perhaps most evident in the group of cases which have now been separated as 'nephrosis'. In these the metabolic upset is severe and the renal functional upset minimal, whilst the osmotic pressure reduction is the greatest met with in any disease. It would appear not improbable that the metabolic disorder occurring in nephrosis may exist to a varying extent in all glomerulo-nephritic conditions associated with oedema, and that this disorder, whatever it be, may be the primary cause on the one hand of the formation of oedema, and on the other of the plasma protein concentration reduction and composition change, and so of the osmotic pressure fall.

It is difficult to believe that the sudden onset of oedema which occurs in acute nephritis is preceded by a sudden fall in osmotic pressure; the evidence, such as it is, goes to show that oedema occurs first and that osmotic pressure falls later and more gradually. In the subacute cases, where the oedema-producing factor still acts, the osmotic pressure remains low, and does not rise until scarring of the kidney sets in, indicating, probably, cessation of the previously active primary pathological process.

The evidence, then, which is at present available, is inadequate to establish a causal relation between nephritic oedema and osmotic pressure changes, or, on the other hand, to rule out the possibility that both are coincident effects of a primary underlying cause.

Summary.

1. The technique of Verney has been employed to determine the osmotic pressure of blood-plasma proteins in nephritis.

By this technique the normal osmotic pressure is 30–32 cm. water.

2. Variations in protein osmotic pressure from 20 to 45 cm. of water may be encountered in general disease states.

3. In non-oedematous nephritis the protein osmotic pressure is unreduced, except slightly just before death; it may, however, be higher than normal, though this rise is not necessarily associated with high blood-pressure.

4. In nephritis with oedema, a definite fall in protein osmotic pressure occurs, and this disappears coincidently with the subsidence of the oedema.

5. In cardiac failure the protein osmotic pressure may be undiminished when oedema is present, or may be found markedly lowered in the absence of demonstrable oedema.

6. The relation of the 'unit' osmotic pressure of the blood protein to the A/G ratio is such as could be theoretically derived by ascribing to the albumin and globulin fractions widely different empirical 'unit' osmotic pressures.

In conclusion, I wish to express my indebtedness to Professor Verney for his demonstration of the technique and frequent help during this work.

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THE TONSIL-ADENOID OPERATION AND SOME OF ITS RESULTS[1]

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The following report is based upon the results of an analysis of the medical records of a group of girls in respect of the state of the tonsils, and deals with the relationship of this to various states of health and with questions arising in connexion with the tonsil-adenoid operation. The records were obtained on the examination of 424 girls as they were admitted to a boarding-school for girls. The pupils are drawn from the professional and well-to-do classes of the community. The information is of value for comparison with data obtained from children of the same age in other strata of society. The ages of the girls are shown in the following table:

Table I.

Ages	12	13	14	15	16	
All cases	3	176	198	43	4	= 424
Operation cases	2	78	86	15	1	= 182
No operation (*a*) 0, L_1, L_2	1	48	70	16	3	= 138
(*b*) L_3	0	26	29	7	0	= 62
(*c*) L_4 and L_5	0	24	13	5	0	= 42
Total. No operation	1	98	112	28	3	= 242

The size of the tonsils was estimated in each case by inspection with the tongue depressed and the throat at rest. In order to attain a comparative degree of accuracy the size of tonsils was recorded in six degrees of visibility, and, for brevity, signs were used for these. The degrees and the signs used for these were as follows:

Tonsil not visible = 0.
Tonsil just visible = L_1.
Tonsil visible half-way to the posterior pillar of the fauces = L_2.
Tonsil reaching the posterior pillar = L_3.
Tonsil extending beyond the posterior pillar = L_4.
Tonsil reaching the uvula = L_5.

[1] Received August 1, 1928.

This sign was preceded by R. in the case of the right tonsil, L. in the case of the left.

The signs will be used throughout this paper with these meanings.

A criticism which is often advanced against this method of estimating the size of the tonsils is based upon the known variations in depth of the tonsillar fossa. This variation makes it impossible to gauge the size of the tonsil by inspection in an individual. But the criticism does not apply to the results obtained from the examination of groups of persons. For, when sufficiently large groups are compared, the error due to this cause becomes a constant common to each group, the same proportion of deep fossae occurring in each. Since the fossa varies from extreme depth to extreme shallowness, as many large tonsils will appear small from this cause as small tonsils will appear large. I have reason for assuming that the errors due to this cause do not exceed more than 10 per cent., because among 242 cases in which no operation has been performed the tonsils were invisible in only 6·6 per cent. A similar argument is applicable to the errors arising from the sessile and pedunculated types of tonsil. In those cases in which eradication has been performed the resulting contraction of scar tissue is such that the whole fossa is readily visible.

A second criticism of my results may be advanced. Throughout this paper a comparison is made between those who have had the tonsil-adenoid operation and those who have not. It may be argued that this comparison is unfair, since among those not operated on there exist all classes of tonsils. The group is therefore a mixed one, and may be considered unsuitable for comparison with the group 'operated on', on the assumption that all individuals in the latter must have had tonsils which were unhealthy. One of the main contentions advanced in this paper is that this assumption is unwarranted. Facts are put forward which indicate that those operated on also constitute a mixed group, consisting partly of those whose tonsillar state necessitated operation and partly of those in whom operation was unnecessary. Among the group 'not operated on', on the other hand, there are undoubtedly many individuals whose tonsillar state would in the opinion of many authorities demand operation. The comparison of these two groups is therefore, in my opinion, justified. It will be shown that when these two groups are contrasted no manifest benefit can be shown to accrue to the group of those operated on. Yet there can be no doubt that some of the individuals derived marked benefit from the operation. Since, however, this benefit is not reflected in the group result, it may be concluded that these individuals formed but a small proportion of the group, and that therefore an operation rate of 42 per cent. (in the case of the population here investigated) and 70 per cent. (1) (in the case of Eton boys) is excessive.

The state of the tonsils found among 424 girls of from thirteen to fifteen years of age is summarized in the following table:

TABLE II.

424 girls.

On admission to school, aged 13 to 15.

State of Tonsils.

I. 182 girls gave history of *operation* = 42·9 %.

A. *No tonsil visible* 84 = 46·1 %.

(*Note.* Two or more operations had been performed in five of these.)

B. *Tonsil visible* 98 = 53·8 %.

Asymmetrical	65	(1) One tonsil visible		49	50 %	Unilateral	49
		(2) Both visible.	Unequal	16	16·3 %		
Symmetrical	33	(3) „ „	Equal	33	33·6 %	Bilateral	49

II. 242 girls gave history of *no previous operation* = 57·07 %.

A. *No tonsil visible* 16 = 6·6 %.

B. *Both tonsils visible and equal* 124 = 51·2 %.

L_1	L_2	L_3	L_4	L_5	
47	*43*	22	12	0	
19·4	17·7	9·9	4·9	0 %	of 242

C. *Tonsils unequal* 102 = 42·1 %. Notes (1) and (2)

L_1	L_2	L_3	L_4	L_5	
10	*22*	40	29	1	
4·1	9·09	16·5	11·9	0·4 %	of 242

Note. (1) Classified according to the *larger* tonsil.
(2) Only one tonsil was visible in 15.
(3) Taking all tonsils of visibility L_3 or less as not enlarged, there remain in the class 'no previous operation' 42 cases with large tonsils = 17·4 %.

I would specially direct attention to the following facts: 1. The high frequency of the tonsil-adenoid operation. 2. The frequency of recurrence of tonsillar tissue after operation. 3. The frequency of inequality in size between the tonsils on the two sides (asymmetry). In every instance the tonsillar operation was accompanied by removal of adenoids. I have no information as to whether the nasal or tonsillar state determined operative interference.

By excluding class L_3 (i.e. tonsils intermediate in size in the group in whom no operation was done), tonsils may be divided into small tonsils (57 per cent.), large tonsils (18 per cent.), intermediate tonsils (25 per cent.). The exclusion of this intermediate class was adopted as a device to separate clearly small from large tonsils.

Significance of Asymmetry of Tonsils.

I distinguished symmetrical from asymmetrical development of the tonsils in the series because I supposed that the larger of two tonsils might be the more diseased. In order to determine this I compared the state of the tonsils with the corresponding state of the anterior cervical glands. This revealed no indication that the larger tonsil is necessarily the more diseased. Thus among 66 cases of asymmetrical recurrence after operation, 38 (57·5 per cent.) showed no glandular enlargement, and 15 (22·7 per cent.) showed glands either just palpable or equally enlarged upon both sides. That is to say, in 80 per cent. of the cases showing

asymmetrical recurrence of tonsils the state of the glands was symmetrical. Of the remainder 6 showed the larger gland on the side of the larger tonsil, 5 showed the larger gland on the side of the smaller tonsil, 1 showed a scar on the side of the larger tonsil. It may be concluded, then, that the larger of two tonsils is not necessarily the more diseased. In fact, it is evident that enlargement of a tonsil is no proof that it is diseased. The enlargement as a rule is due to an increase in the number and activity of the germinal follicles and is a physiological activity in response to some stimulus of the nature of which we are ignorant.

Associated Maladies.

Certain conditions were selected for correlation with the state of the tonsils because each has been held, by one observer or another, to have some association

TABLE III.

Tonsil no operation contrasted with Operation — 242 cases. 182 cases. Total 424 cases.

	No Operation.				Operation.		All Cases.	
	Sym-metrical.	Asym-metrical.	Total.	%.	Total.	%.	Total.	%.
Total.	140	102	242		182		424	
Teeth bad	52	51	103	42·5	94	51·6	197	46·4
Glands enlarged	17	22	39	16·1	21	11·5	60	14·1
Bone deformity	4	4	8	3·3	8	4·3	16	3·7
Defective vision	26	24	50	20·6	48	26·3	98	23·1
Rheumatism	6	10	16	6·6	22	12·08	38	8·9
Heart abnormal	4	6	10	4·1	7	3·8	17	4·0
Defective hearing or otorrhoea (history of)	18	6	24	9·9	27	14·8	51	12·02
Postural spinal defects	41	30	71	29·3	60	32·9	131	30·8
Flat-foot	9	10	19	7·8	25	13·7	44	10·3
Healthy appearance	—	—	—	75·8	—	68·6	—	—

with tonsillar disease, and because each was recorded in my series. The incidence of these is set out in Table III. The headings are used in the following senses:

Teeth bad means that four or more teeth showed caries.

Glands enlarged refers only to the anterior cervical glands and includes any enlargement which was easily palpable.

Bone deformity refers to bow-leg, knock-knee, or chest deformity (Harrison's sulcus and pigeon-breast).

Defective vision was determined by Snellen's distance test types.

Rheumatism. Under this heading was included any girl who gave a history of pain in joints, growing pains, or muscular rheumatism.

Heart abnormal. If on examination any abnormality of size, sounds, or rhythm of the heart was detected the case was included under this heading.

Defective hearing or otorrhoea. All cases giving a history of otorrhoea

were included and any cases showing the slightest evidence of defect of hearing. There were no cases of chronic otorrhoea in the group.

Postural spinal defects. Any girl showing round shoulders or any trace of lateral curvature of the spine was included under this heading provided the deformity could not be voluntarily corrected with ease.

Flat-foot. I included under this heading any girl who exhibited what appeared to be a poor arch on standing.

Healthy appearance. I excluded from this group any individual who looked delicate, was unduly thin or unduly fat, or who had pallor of lips or conjunctivae, or a 'muddy' complexion.

The conditions enumerated may be considered as having local or general associations with tonsillar enlargement as follows:

1. Local associated conditions.
   - (*a*) Enlargement of the anterior cervical glands.
   - (*b*) Deafness and otorrhoea.
   - (*c*) Dental caries.
   - (*d*) State of the lymphoid tissue of the nasopharynx.
2. General associated conditions.
   - (*a*) Debility.
   - (*b*) Certain general diseases.
     - (i) The exanthemata.
     - (ii) 'Rheumatism'.
     - (iii) Rickets.

They will be considered in that order.

1. *Local Associated Conditions.*

(a) *Enlargement of the anterior cervical glands.* The tonsils are known to drain into the deep glands of the upper part of the neck. These glands, and especially the tonsillar gland, enlarge in association with acute or chronic infections of the tonsils. The frequency of enlargement of these glands among the various groups in my series is shown in the following table:

TABLE IV.

State of Tonsils compared with Enlargement of Anterior Cervical Glands.

	Tonsils.	0.	L_1.	L_2.	L_3.	L_4.	L_5.	Totals.
No operation on tonsils	Glands enlarged	2	4	13	12	7	1	39
	Glands not enlarged	14	53	52	51	33	0	203
	Totals	16	57	65	63	40	1	242
Operation on tonsils	Glands enlarged	9	6	3	1	1	0	20
	Glands not enlarged	75	47	28	8	4	0	162
	Totals	84	53	31	9	5	0	182

It will be observed that enlargement of the anterior cervical glands is commoner, firstly, with large than with small tonsils in those not operated upon, the percentage incidence being 13·7 per cent. in the combined classes 0, L_1, and

L_2 (138 cases), 19·0 per cent. in the intermediate class L_3 (63 cases), 19·5 per cent. in the combined classes L_4 and L_5 (41 cases); secondly, among those whose tonsils are intact (16·1 per cent.) than among those in whom they have been removed (11·4 per cent.).

Among those operated on the completeness or incompleteness of the enucleation does not affect the incidence of enlarged glands. Thus among 86 cases with no recurrence of tonsillar tissue enlarged glands were present in 11·6 per cent., and among 97 cases of recurrence in 11·3 per cent. From this it may be concluded that the lymphoid tissue regenerated after operation is not infective in character. The removal of tonsils, then, lowers the incidence of enlarged glands in the neck, as might be expected. But it is noteworthy that in spite of the operation enlarged glands were still present in 11·4 per cent. of all the cases. It is evident that infection can reach them from other sources, e.g. the teeth.

(b) *Deafness and otorrhoea.* In this study these defects are considered from the standpoint of their relation to the tonsil-adenoid operation. Deafness and otorrhoea were included in the inquiry because enlargement of the tonsils and adenoid hypertrophy are so commonly associated, and because adenoids are believed to be an aggravating cause of otitis media, the removal of adenoids being often advocated in cases of recurrent earache and of otorrhoea. In my series of cases in which the tonsils were removed, adenoids also were operated upon in every instance. There is no information as to whether the nasal or the tonsillar state determined operation interference.

Of the 182 cases subjected to the tonsil-adenoid operation 23 (12·6 per cent.) gave a history of otorrhoea. In 4 of these cases the relative dates of the operation and of the otorrhoea were not ascertained. Of the remaining 19 cases, however, as many developed otorrhoea after the operation as before it. Thus otorrhoea occurred subsequent to the operation in 10, in the same year as the operation in 5, and before the operation in 4.

It is presumed that, in those in whom the two events are recorded in the same year, the operation was performed subsequently to and for the relief of the otorrhoea. Of those in whom the otorrhoea appeared subsequent to the tonsil-adenoid operation 4 showed tonsils just visible (L_1), and in the remainder no tonsillar tissue could be detected. It may be alleged that the operation prevented otorrhoea in many of the cases. It is impossible to confute such a statement, but it is significant that of 242 girls whose tonsils and adenoids had not been surgically treated only 5·3 per cent. gave a history of otorrhoea as against 12·6 per cent. of those in whom the operation had been performed.

It remains to consider the incidence of defects of hearing (deafness). This is shown in the following table:

TABLE V.

		Otorrhoea.	No Otorrhoea.	Totals.
Operation 182	Deaf	6	4	10 = 5·5 %
	Not deaf	17	155	172
No operation 242	Deaf	4	9	13 = 5·3 %
	Not deaf	0	220	229

The incidence of defect of hearing was similar in the classes 'operation' and 'no operation'. In those who suffered from otorrhoea the incidence was greater among those not operated on as 30 per cent. is to 26 per cent. In those who had not suffered from otorrhoea the incidence of defective hearing was 2·5 per cent. in those operated on and 3·9 per cent. among those not operated on. The size of the tonsils in those not operated on did not appear to be related to the incidence of defective hearing, as is shown in the following table:

TABLE VI.

Classes of tonsils	0	L_1.	L_2.	L_3.	L_4.	L_5.	Totals.
Totals in each class	16	57	65	62	41	1	242
Deafness and no otorrhoea	0	3	3	1	2	0	9
Deafness and otorrhoea	1	0	1	2	0	0	4
Totals	1	3	4	3	2	0	13

Lastly, the figures for deafness and otorrhoea combined (shown in Table III) show a distinct preponderance of these conditions among those whose tonsils and adenoids had been surgically treated.

The removal of adenoids is commonly advised in cases of earache, and this may be, and often is, followed by a cessation of recurrent attacks as a result of the removal of infected mucosa and lymphoid tissue. It may also provide drainage for a suppurating middle ear whose Eustachian tube has hitherto been obstructed; but it is obvious that the mucosa and its lymphoid tissue (whether pathological or not) will be replaced by scar tissue, which, in addition to having a low resistance to infection, may, by its subsequent contraction, again increase liability to infection of the middle ear by constricting or widening the Eustachian stoma. This may be the explanation of the occurrence of otorrhoea after the adenoid operation. If, on the other hand, this is due to regrowth of the adenoid tissue in persons liable to lymphoid hypertrophy, the efficacy of the operation as a preventative of otitis media must be seriously challenged. There are many valid reasons for removing adenoids, but I submit, in view of the above figures, that prevention of otorrhoea is not one of them.

(c) *Dental caries.* The incidence of dental caries in my series is shown in the following table:

TABLE VII.

Size of Tonsils.		0	L_1.	L_2.	L_3.	L_4.	L_5.	Totals.
Operation	Bad teeth	57	31	14	6	3	0	111
	Good teeth	27	22	17	3	2	0	71
	Totals	84	53	31	9	5	0	182
No operation	Bad teeth	5	24	26	28	19	1	103
	Good teeth	11	33	39	35	21	0	139
	Totals	16	57	65	63	40	1	242

That there may be some direct association between dental caries and tonsillar hypertrophy is not improbable. On the one hand, carious teeth may act as a source of infection to the tonsils, while, upon the other hand, inefficiency of the

tonsils as disinfectors of the mouth may favour the occurrence of caries. Such an association might be related to age, since it is known that caries and tonsillar enlargement seldom occur in adults, being replaced by pyorrhoea and tonsillar atrophy respectively. Analysis of the figures, however, suggests that the relation may be a direct one, independent of the question of age. Of those not operated on 42·5 per cent. had bad teeth as against 60·9 per cent. of those who had been subjected to the tonsil-adenoid operation. Of 138 girls with small tonsils (0, L_1, L_2), 39·8 per cent. had bad teeth, and of 41 girls with large tonsils (L_4 and L_5), 48·7 per cent. had bad teeth. It would appear, then, that the frequency of caries rises as the evidence of tonsillar enlargement increases. It has already been pointed out that tonsillar tissue was frequently present after operation. 55·1 per cent. of these individuals had bad teeth. Among those, on the other hand, who showed no tonsillar tissue after operation, the percentage showing bad teeth was 67·8 per cent. When these figures are compared with the 42·5 per cent. bad teeth found among those whose tonsils were intact it is difficult to resist the conclusion that the state of the teeth and that of the tonsils are directly interrelated. The figures suggest, though they by no means prove, that the presence of tonsillar tissue may be a factor in the prevention of caries. On the other hand, the presence of caries may be one of the causes of tonsillar hypertrophy. This view is held by some authors. Guthrie (2), for example, advises attention to the teeth before definitely deciding upon a tonsillectomy.

(d) *State of the lymphoid tissue of the nasopharynx.* It is known that tonsillectomy is apt to result in overgrowth of adenoids, and for that reason the removal of the adenoid tissue of the nasopharynx is advocated whenever tonsillectomy is performed. Such overgrowth may be regarded as a compensatory hypertrophy. A similar compensatory hypertrophy of lymphoid issue in the pharynx tends to follow the complete tonsil-adenoid operation. Thus, in those on whom no operation had been performed, granular pharyngitis was present in 24·8 per cent.; in those on whom *operation had been performed,* and in whom tonsillar tissue was still present, the percentage of granular pharyngitis rose to 30·7 per cent.; while in those in whom eradication had been complete it was present in 38·1 per cent. It is evident, then, that the tonsil-adenoid operation is followed by compensatory hypertrophy of the lymphoid tissue of the pharynx.

2. *General Associated Conditions.*

(a) *Debility.*

The view is held by some that tonsillar hypertrophy is associated with (and may be the result of) a debilitated state of the general health. I cannot find anything in my results to support this view. The facts which I have already referred to point to local infection as one cause of tonsillar hypertrophy. It must be admitted that a condition of debility will favour oral sepsis and to that extent may result in compensatory increase in size of the tonsils.

As evidence of debility, postural spinal defects were selected because they

are believed to occur commonly in debilitated persons, and visual defects were also investigated in this connexion. Both of these are slightly commoner in the group whose tonsils were removed than among those whose tonsils were not removed. Comparison between those with small tonsils and those with large tonsils shows no difference in incidence of postural defects (28·9 per cent. and 30·9 per cent. respectively) or of visual defects (26·8 per cent. and 28·5 per cent.). Neither of these defects show variations in incidence with variations in size of tonsils. The slight preponderance among those operated upon does no more than suggest that that group was composed of less healthy individuals than the average. There is therefore no evidence to show that the operation acted beneficially in respect of postural defects or visual acuity.

(b) *Certain General Diseases.*

(i) *Tonsils and the exanthemata.* One view in regard to the functions of the tonsils is that they serve as auto-vaccination stations concerned with the production of specific antibodies. Is there any evidence that their action is responsible for the specific immunity which we know to follow many of the exanthemata? No evidence, so far as I am aware, has ever been produced to support this. The only evidence that would be conclusive would be facts to show that persons whose tonsils had been completely eradicated failed to develop immunity after subsequent attacks of the exanthemata. Such evidence could only be produced by following a large number of cases for a large number of years.

Another view of the function of the tonsils is that they are phagocytic stations engaged in destroying infective particles. If they act in this way in regard to the exanthemata we would expect to find a greater liability to these diseases among those in whom the tonsils have been completely eradicated. To demonstrate this is not so simple as it appears, because a great number of children have suffered from several of the exanthemata before their tonsils were removed, so that their liability is correspondingly diminished. In a fully established epidemic of measles or rubella very few individuals in a community who are not protected by a previous attack escape. Thus in one epidemic, of 100 girls who had not had measles 98 got it, while of 200 previously protected 198 escaped. That is to say, the infection appeared to be quite independent of the existence or absence of tonsils. If, on the other hand, the tonsils form a specially favourable port of entry we should expect to find some immunity in those who had had their tonsils completely removed. I can find no evidence of this. E.g. C. G. had her tonsils removed in 1915 at the age of 4. When seen by me at the age of 14½ there was no trace of tonsillar tissue remaining. Yet in the interval she had suffered from measles, whooping-cough, mumps, scarlet fever, and chicken-pox.

An analysis of 44 cases in whom the tonsils had been removed and in whom no tonsillar tissue was present at the time of examination shows that subsequent to the date of operation only 17 escaped all the exanthemata, and in the majority of these the date of operation was quite recent.

It may therefore be concluded that the tonsils have no effect upon the incidence of the exanthemata and that their total removal does not increase or diminish the liability to those diseases.

(ii) '*Rheumatism*'. The terms 'rheumatism' and 'rheumatic' are so loosely applied that in recording the histories given by groups of persons it is impossible to differentiate the diseases included by them under this term. True rheumatism in its more severe forms is distinguished by the term 'rheumatic fever'. In its less severe forms it is seldom distinguished from other forms of arthritis, being included with them under the general term 'rheumatism'. Under the heading rheumatism the cases are divided into the following groups:

Growing pains, R_1; pains in joints without fever, R_2; pains in joints with slight fever, R_3 = subacute rheumatism; rheumatic fever, R_4; severe rheumatic fever, R_5.

True rheumatism is rare among the class of girls who attend this boarding-school, for among 424 only 8 gave a history of joint pains with fever—5 among those whose tonsils had been removed and 3 among those whose tonsils had not been removed. Only one of those girls described her disease as *rheumatic fever*. The attack followed scarlet fever, was succeeded by no permanent cardiac damage, and, after its subsidence, by no recurrence of rheumatic manifestations. It seems possible that it was an example of septic arthritis. This illness occurred subsequently to a tonsil-adenoid operation. There is no evidence in these figures of an association between true rheumatism and tonsillar hypertrophy.

TABLE VIII.

	Tonsillitis.	No Operation.	242 cases correlated with Rheumatism.				
Classes	0	L_1.	L_2.	L_3.	L_4.	L_5.	Totals.
Totals	16	57	65	63	40	1	242
0	13	32	43	36	31	1	156
R_1	3	22	18	19	4	—	66
R_2	—	1	3	5	4	—	13
R_3	—	1	1	1	—	—	3
R_4	—	—	—	—	—	—	—
R_5	—	—	—	—	—	—	—

In Table VIII the results obtained from 242 girls whose tonsils had not been removed are shown. It will be observed that the three cases of arthritis with fever show no special predilection for one or other group of tonsils. But the group R_2 (i.e. those with joint pains and no fever) becomes more frequent among those with the larger tonsils. Reducing these figures to percentages of their groups, we find 1·7 per cent. of R_2 in group L_1, 4·6 per cent. in group L_2, 7·9 per cent. in group L_3, 9·7 per cent. in groups L_4 and L_5 combined. It is generally admitted that many of these low forms of arthritis are dependent upon toxic absorption from a septic focus, and this table suggests that the larger the tonsil the greater is the probability that it may form such a focus.

On reducing the group 'growing pains' to percentages it is readily seen that they bear no relation to either the size of the tonsil or the occurrence of afebrile arthritis. I suggest that the figures show some evidence in favour of

the view that the tonsil may form a focus for absorption of toxins capable of producing arthritis, and that the larger the tonsil the greater is this probability.

(iii) *Rickets.* Recently an observer, to whose figures I have had access, from statistical material collected from board schools in a colliery district of Durham, concluded that 'there is so close an association between the presence of rickets and the development of enlargement of the tonsils and adenoids . . . that it is impossible to dissociate them'. He unfortunately does not define what he means by enlargement of the tonsils, but he requires as evidence of rickets the presence of two of the following signs: 1. Parietal bossing. 2. Frontal bossing. 3. Bony changes of the chest wall, namely, Harrison's sulcus or pigeon-breast. 4. Bow-leg. 5. Knock-knee. He found that of 2,676 children examined by him only 6 per cent. showed no evidence of rickets. He subdivides his cases into groups according to sex and age. His group of 12-year-old girls numbers 446, so that it is a convenient one for comparison with my group of 424 girls of from 13 to 15. He found that 73 per cent. of this group showed certain evidence of rickets, and that of these bow-leg was present in 11·5 per cent., knock-knee in 42·9 per cent., chest deformities in 24·9 per cent. Among my group, if all these deformities are combined together, they occur in only 3·5 per cent. of the members. This percentage becomes higher (6·5 per cent.) if only those are selected whose tonsils have been removed or who show definite tonsillar enlargement. It is evident from these figures that the prevalence of rickets, as indicated by these signs, is very much lower among my group than among his. If his hypothesis is correct, my series should show a proportionally lower incidence of enlargement of the tonsils than his. Yet only 17·4 per cent. of his girls showed enlargement of tonsils, while 42·9 per cent. of mine had had their tonsils removed, and of the remainder 17·7 per cent. showed tonsils extending beyond the posterior pillars of the fauces. Among girls of the well-to-do classes, then, it is evident that, though rickets is much rarer, enlargement of the tonsils is more frequent. It may, therefore, be concluded that rickets has no close association with the prevalence of enlargement of the tonsils. He also considers that dental caries is closely associated with rickets. He found more than four teeth decayed in 30·9 per cent. of his girls. In my series 46·4 per cent. showed more than four teeth decayed, though my proportion of rickets is so much lower than his. Though enlargement of tonsils and rickets do not appear to be associated, there may be (and apparently is), as I have pointed out, a direct association between caries and tonsillar enlargement. It is a fact of the utmost importance that caries and enlargement of tonsils are much more frequent among my group of well-to-do children than among his group of colliery children, and it is a fact which demands thorough investigation. What factor is active in both groups but much more active among the well-to-do?

Function of the Tonsils.

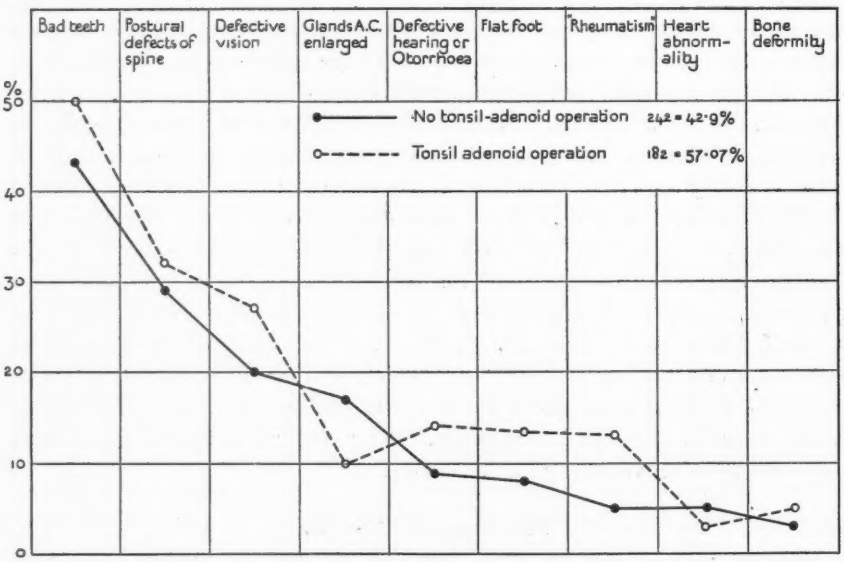
We are ignorant of the function of the tonsils. They consist almost entirely of a subepithelial collection of lymphoid tissue which surrounds infoldings of

the epithelium. These constitute the crypts of the tonsil. Solid particles, including bacteria, find their way into the substance of the tonsils from the surface and from the crypts, by what agency is not known. It is believed by some that they are carried in by the lymphocytes. Within the tonsil bacteria may be destroyed, by the phagocytic action of polymorphs or endothelial cells, or may persist, when they give rise to foci of disease. When the resisting mechanism of the tonsil breaks down, organisms or their products pass by the lymphatics to the tonsillar lymphatic gland and cause its enlargement.

It is assumed by those who advocate complete eradication that the functions of the tonsil are of little importance, but there are many reasons against such an assumption.

1. The tonsils have a free blood supply derived from three sources.
2. They have a double nerve supply.
3. They occur only in mammals.
4. In man they are specially active during childhood.
5. They contain many active germinal centres for the manufacture of lymphocytes.
6. Their removal is followed by hypertrophy of neighbouring lymphoid tissue.

With these findings in mind, let me again draw attention to the arresting fact that 42 per cent. of the girls admitted to this school have had the tonsil-adenoid operation performed before the age of fourteen. The following graph summarizes the results of my examination of these girls on admission. It compares the percentages of the various defects I have referred to in the two great groups Operation and No Operation.



Incidence of Defects.
Tonsil-adenoid operation compared with no operation.

It is evident that those subjected to the operation were not only no better than the rest, but were actually worse in practically every particular with the exception of enlarged cervical glands. But it is also important to note that even among those whose tonsils and adenoids had been removed, enlargement of these glands was found in 11 per cent. I have indicated that the removal of adenoids results in an increased incidence of otorrhoea, and that in several respects those in whom removal of tonsils was complete are worse off than those in whom it was incomplete.

While it is undoubted that in a considerable number of cases great benefit results from the tonsil-adenoid operation, in view of these facts it is evident that a more conservative method of dealing with many of the cases must be devised, and especially that attempts should be made to discover some method, other than surgical removal, of dealing with adenoid overgrowth in the nasopharynx.

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2. Guthrie, *Diseases of the Ear, Nose, and Throat in Childhood*, 1921, p. 65.

ADDISON'S DISEASE WITH ATROPHY OF THE CORTEX OF THE SUPRARENALS[1]

By O. BRENNER
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With Plate 5

In 1894 Oliver and Schäfer showed that the medulla of the suprarenals contained adrenalin, which has very striking properties, while the cortex yielded no substance with any recognizable action. It was, therefore, assumed by many observers that the fatal results of extirpation of the suprarenals and the symptoms of Addison's disease were due to lack of adrenalin. It is only in recent years that it has been realized that the cortex is, after all, of great importance. The cases recorded below may perhaps throw some light on this point.

Case 1. An unmarried and slightly built woman of 32, admitted to hospital on November 11, 1926. She said that she had always been 'delicate'. In 1919 she had an attack of pleurisy. In 1922 her appendix was removed for chronic appendicitis. In 1923 she had pneumonia. In 1924 she had 'gastric 'flu'. After this she was well till three weeks before admission, when she noticed that she had recently become very brown. A few days later she began to feel weak and giddy, and had to go to bed. She also began to vomit both after food and independently of food. She twice tried to return to work, but each time was too weak.

On admission, the skin of the face and neck was generally bronzed, with a few small deep brown patches. The areolae of her breasts and the front of her knees were deep brown, and there was a patch of pigmentation where the corsets had rubbed. There was a small patch of bluish pigmentation on the left side of the soft palate. The blood-pressure on admission was 70/56. During her stay in hospital the systolic pressure was never found above 90, nor the diastolic above 65. Towards the end the systolic pressure fell to 58 and the diastolic became unreadable. No abnormality was found in the respiratory, alimentary, nervous, or genito-urinary systems. The blood count and differential leucocyte count showed no abnormality. Wassermann reaction not tested.

She was treated by means of hypodermic injections of liq. adren., the dose being increased up to 100 minims daily. In addition, she was given up to 21 gr.

[1] Received May 22, 1928.

daily of suprarenal whole gland extract by the mouth. In spite of this she steadily went downhill. Vomiting continued, the blood-pressure fell, and she became progressively weaker. She died on January 23, 1927. The total duration of her symptoms was thus about three months.

At necropsy the subcutaneous fat was deep yellow in colour. There was an old calcified tuberculous focus at the apex of the left lung. The heart showed brown atrophy and weighed only 170 grm. No abnormality, naked eye or microscopical, was found in the alimentary tract, liver, spleen, kidneys, or brain. The suprarenals were very small and appeared as brownish shreds embedded in fat. The thyroid gland was rather smaller than normal and weighed 25 grm., but showed no other abnormality to the naked eye. The pituitary, pancreas, and ovaries showed no naked-eye change. No thymus was seen. The solar plexus on each side showed no abnormality.

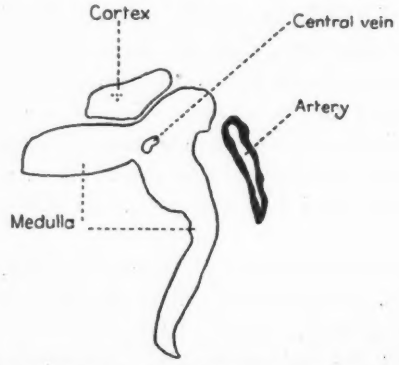


FIG. 1. Suprarenal from Case 1. ×4. This outline drawing shows the relative amounts of cortex and medulla present. The medulla is present in at least normal amount, while there is only one small island of degenerate cortical tissue present.

Microscopically, the suprarenals show thickening of the capsule. The cortex is much reduced, and in some of the sections is completely absent, the fibrous capsule lying directly on the medulla. What cortex remains is in the form of small nodules, often widely separated from each other. The cells, which are very loosely and irregularly arranged, are mostly enlarged and bloated looking, and stain pink with haemalum and eosin. The nucleus is usually small and vesicular, with one or two nucleoli: the cytoplasm is finely granular. Various stages in the degeneration of these cells can be seen. Vacuoles appear in the cytoplasm and increase in size until there is left only the delicate cell membrane, sometimes containing the remnants of cytoplasm and a vesicular nucleus, sometimes quite empty. Large spaces between the cell-groups are formed in this way by the disappearance of some of the cells. In some places all the cells have disappeared, leaving only the fibrous stroma containing many capillaries. This has produced a septum of vascular connective tissue between the medulla and cortex. The medulla is little affected, and is not reduced in amount. It makes up the bulk of the suprarenal (see Fig. 1). It consists of irregular columns

of cells staining deep purple and separated by blood sinuses. It contains a few small groups of ganglionic nerve cells. A number of small normal-looking sympathetic ganglia are present in the capsule of the glands. Foci of infiltration with lymphocyte-like cells are present beneath the capsule and in the boundary zone between the cortex and medulla.

The thyroid gland shows intense infiltration with lymphocyte-like cells, with wide separation of the vesicles, which are greatly reduced in number and size, lined with flat or cubical epithelium, and contain very little colloid.

The anterior lobe of the pituitary shows a preponderance of small eosinophil cells. There are a few colloid-containing pseudocysts.

The ovaries and pancreas show no marked change.

The semilunar ganglia of the solar plexus show no abnormality. The normal amount of pigment and fibrous tissue is present on comparison with other, presumably normal, ganglia.

Case 2. A married woman of 47, who had suffered a severe mental shock a year before death. Thenceforth she complained of dyspepsia with occasional vomiting, and steady loss of strength, finally causing her to keep to her bed. Her skin became progressively darker. She was found dead in bed.

At post-mortem the body was thin. There was pigmentation of the skin, most marked on the face, with darker patches on the back of the wrists and hands. The heart showed brown atrophy. There was a general atrophy of the stomach and bowel. The suprarenals were small and thin, the two together weighing only 4·6 grm. instead of the normal 10 to 12. The other organs showed no naked-eye change.

Microscopically, the left suprarenal shows no thickening of the capsule. The medulla is normal in amount, and, apart from congestion, appears normal. The cortex is greatly reduced, and in places has disappeared, so that the capsule rests directly on the medulla. It is present in small isolated islands, bearing no resemblance either in the nature or in the arrangement of their cells to normal suprarenal cortex. The cells are loosely and quite irregularly arranged. Most of them are several times the normal size. The nucleus is usually small and vesicular (though it is sometimes large and hyperchromatic) and often contains several nucleoli. Some cells have two, three, or even four nuclei, while others seem to have none at all. This is probably due to the fact that, owing to the great size of the cell compared with the nucleus, the plane of the section passes through the cell but misses the nucleus. The cytoplasm stains pink with eosin. In the less affected cells it is finely granular. In others small vacuoles appear, increase in size, coalesce, and finally result in the destruction of the cells. The loose arrangement of the cells is due to this process of disintegration by vacuolation. The spaces between the cells have been left by the disappearance of some of the large bloated cells, and some of the spaces still contain a little pink-staining granular debris representing the remains of the cytoplasm. All stages from the large hyperactive-looking cells with large hyperchromatic nuclei to those spaces containing only granular debris can be seen. Here and there are a few

small cortical cells more like the normal. There is no increase in the interstitial connective tissue. Everywhere in the cortex there is much blood, some lying free, some in the engorged capillaries and veins. In some areas there are only a few degenerate cortical cells, the rest of the tissue consisting of a delicate connective tissue network in the meshes of which are many red blood cells. Some areas consist entirely of dilated capillaries and veins separated by connective tissue. Elsewhere there are occasional cortical cells embedded in masses of lymphocyte-like cells. Two large recent haemorrhages destroy large portions of the cortex. The large arteries and veins in the peri-suprarenal fat and inside the gland are engorged but show no other change. No sympathetic ganglia appear in the sections, but there are in the medulla a number of large normal-looking nerve-bundles.

The right suprarenal was cut into five strips, each 3 or 4 mm. broad, and several sections were cut from each end of each strip. By these means only two small islands of cortex were discovered. The rest of the suprarenal consists of medulla which mostly lies directly beneath the capsule, though in some places it is separated from it by a layer of haemorrhage. The cells in the cortical islands are little larger than normal, and are quite unlike the enormous bloated cells of the cortex of the left suprarenal. There is much lymphoid infiltration of the cortical islands. The medulla is normal in amount, and, apart from some congestion, appears normal. It contains many large normal-looking nerve-bundles.

The semilunar ganglion contains many dilated blood-vessels. There is no increase in the pigment in the ganglion cells or in the amount of interstitial fibrous tissue.

Case 3. A man of 34, admitted to the General Hospital on December 8, 1924. He had had typhoid fever in 1900 and double pneumonia in 1914. In 1922 his skin began to get bronzed, and he slowly lost weight and became weaker, until he had to take to his bed. Later he began to have attacks of abdominal pain. Shortly before admission severe frontal headaches came on. On admission he was found to be thin. The skin was bronzed, especially round the nipples and umbilicus. There were patches of pigmentation in the mouth. No abnormality was found in the alimentary, nervous, or genito-urinary systems. The cardiac impulse and sounds were feeble. The lowest blood-pressure recorded was 90/58, and the highest 110/67. The fasting blood sugar was 0·036 per cent. He died on January 19, 1925.

At post-mortem pigmentation was found as above. There were bilateral pleural adhesions, but no lesion of the lungs. The heart was small, weighing 240 grm., but was normal in colour. There was a fibrino-purulent pericarditis. Both suprarenals, especially the right, were very small. The other organs showed no naked-eye change.

Microscopically the suprarenal capsule shows thickening and infiltration with lymphoid cells. The cortex is greatly reduced in amount and in some sections is practically missing. It consists of a number of islands separated by

thick strands of dense vascular fibrous tissue infiltrated with lymphoid cells. The cortical cells are loosely and very irregularly arranged. They are mostly greatly enlarged, though some of them are no larger than the cells of the normal suprarenal cortex, which they closely resemble. The nuclei are usually small and vesicular, though sometimes they are large and hyperchromatic, and some are pyknotic. Some cells have two nuclei. Most of the cells contain yellowish-brown pigment granules. All stages of degeneration of the cells can be seen. The least affected are several times the normal size, have a fairly homogeneous or finely granular cytoplasm and a large hyperchromatic nucleus, the appearances being suggestive of a hypertrophy of the cell compensatory to the general atrophy. The first stage in the degeneration is a further increase in size and the appearance of vacuoles in the cytoplasm. The cell and the vacuoles increase in size until the cell consists only of a delicate cell membrane, inside which there is a very delicate pink-staining network with a very open mesh, and either no nucleus or one which stains badly. Finally there are left spaces outlined by a delicate pink-staining membrane, apparently the remains of the cell-membrane. There are many such spaces, and they give the loose spongy look to the tissue. In some of the cortical islands the spaces are much more numerous than the cells. In such areas there are many capillaries and a dense infiltration with lymphoid cells. The medulla is normal in amount and seems normal, apart from a few small areas of fibrosis and lymphoid infiltration round the central vein. Some normal-looking nerve-bundles are present, but no sympathetic ganglia appear in the sections.

The thyroid shows some increase in its fibrous stroma and many small lymphoid infiltrations. The vesicles are of medium size, full of colloid, and lined by flat or cubical epithelium.

The testis shows much increase in its fibrous stroma, in which there are many interstitial cells. The seminiferous tubules seem to be fairly normal, but though spermatogenesis is occurring, it is not very active.

The anterior lobe of the pituitary shows a great preponderance of eosinophil cells.

Case 4. A single woman of 27, admitted on 10.4.28 in a semi-comatose condition, and dying two hours later. She had always been pigmented, but had become more so in the last eighteen months. Some years before, she had had a goitre, with prominence of the eyes, 'nervousness' palpitations, and attacks of vomiting and diarrhoea. The goitre disappeared, but the prominence of the eyeballs and the nervousness remained. For eighteen months before admission, she tended to get tired very easily, her pigmentation increased, and her appetite diminished. Since Christmas 1927 she had had many attacks of vomiting and diarrhoea. Fourteen days before admission she had an attack of 'influenza', with headache and pains in the limbs, and vomiting was frequent. She was in bed four days. On April 9 she was well enough to walk in the garden. The next morning she was semi-comatose. Her blood-pressure then was 85 (systolic). She was admitted to hospital at 6.30 p.m. that day in a semi-comatose condition. There

was marked pallor and slight cyanosis of the cheeks and lips. Temperature 95° F. Pulse 120, and very feeble and running. Breathing of the Cheyne-Stokes type. The breath smelt strongly of acetone, and the urine contained much acetone but no sugar and only a trace of albumin. Death occurred at 8.45 p.m. A tentative diagnosis of exophthalmic goitre with a terminal acidosis was made.

At post-mortem the body was that of a slightly built but fairly well-nourished young woman. There was a general brown pigmentation of the skin, most marked over the front of the knees, in the perineum, and on the outer side of each upper arm. Many small deeper brown freckle-like spots were scattered over the skin. The mucous membrane of the gums and tongue showed patches of brown pigmentation. Both sclerotics showed beneath the cornea a wide zone of brownish-black pigmentation. The subcutaneous fat was normal in amount and of a deep yellow colour. The lungs had old healed tuberculous scars at each apex. The heart showed marked brown atrophy, weighing only 165 grm. The aorta was very narrow, being barely one inch in circumference, and the intima of the abdominal portion showed patches of fatty degeneration. The small thymic remnant appeared to the naked eye to consist entirely of fat. The mediastinal glands showed a slight enlargement and marked anthracosis. Two or three caseous partially calcified glands were present in the right iliac fossa. The gastro-intestinal tract, liver, pancreas, spleen, kidneys, and brain showed no obvious abnormality. After a careful search, no definite suprarenal was identified in the fatty areolar tissue at the upper pole of the kidneys, but the tissue was preserved for microscopical examination. Beneath the capsule of the right kidney, on its anterior surface and near its upper pole, there was found what was taken for a small accessory suprarenal. It measured 3 cm. in length, 1 cm. in its greatest breadth, and was of paper-like thinness. No accessory suprarenal was found on the other side, or along the course of the ureter, or in the broad ligament. The splanchnic nerves and solar plexus appeared normal. The uterus and ovaries appeared normal. The thyroid gland weighed 30 grm. and was not obviously enlarged. On section it showed to the naked eye many strands of fibrous tissue. The pituitary appeared normal.

Microscopical examination of the fibro-fatty tissue at the upper poles of the kidneys shows that remnants of suprarenal tissue were after all present, though they were not seen till the fat had been dissolved out in the course of the preparation of the sections. It was then seen that there were very small and thin pieces of suprarenal tissue embedded in the fibro-fatty tissue. The capsule is thickened and consists of dense, rather laminated connective tissue, showing some round-cell infiltration. The cortex is almost completely replaced by dense fibrous and hyaline connective tissue showing many engorged capillaries and many foci of lymphoid infiltration. In one section there is present one very small island of tissue resembling the zona glomerulosa of the normal suprarenal cortex. This island is surrounded by a thick zone of dense fibrous tissue, and shows much increase in its fibrous stroma and foci of lymphoid infiltration.

Apart from this the cortex of both suprarenals is represented only by two or three small groups and narrow strands of large bloated-looking cells with granular cytoplasm containing yellowish-brown pigment and small vesicular nuclei. Most of the sections show no cortex at all, but only dense hyaline vascular fibrous tissue, infiltrated with round cells. Medullary tissue is abundantly present in most sections, and in many sections it seemed to be quite normal, though in some it is densely infiltrated with lymphoid cells. There are present several normal-looking nerve-bundles but no ganglia.

The accessory suprarenal consists of a mass of connective tissue. It is surrounded by a separate and distinct fibrous capsule. In the middle is a large central vein to which the many engorged capillaries run in a radial manner. The connective tissue in parts is dense and hyaline, but elsewhere it is loose and fibrillar and shows many large spaces, outlined by delicate membranes. Some of these spaces are empty, others contain a small round lymphocyte-like cell, and others a little pink-staining granular debris. A very few large bloated cortical cells are present, usually singly or in groups of two or three. The cytoplasm is granular. The nucleus is usually small and pyknotic, though in one or two it is large and hyperchromatic. Most sections contain no cortical cells, and no section contains more than ten. No medullary tissue is present. No chromaffin cells are present. Unfortunately the fibro-fatty tissue in which the remnants of the main suprarenals are found were not fixed in a solution containing potassium bichromate, so that the chromaffin reaction was not obtainable in the medulla.

The coeliac ganglion shows no abnormality. No chromaffin cells are to be seen.

The thyroid gland shows an excess of dense fibrous stroma and a few foci of lymphoid infiltration. The vesicles are mostly of moderate size, lined by cubical epithelium, and are full of colloid. A few vesicles are larger, lined by taller epithelium, and contain no colloid, but are full of desquamated cells.

The anterior lobe of the pituitary shows a great preponderance of basophil cells. The posterior lobe appears normal. No abnormality is seen in the pancreas or ovaries. Remnants of thymic tissue are present embedded in fibro-fatty tissue. Atrophic Hassall's corpuscles are present, with numbers of calcareous granules. The lymph glands show some hyperplasia of the lymphoid and to a less extent of the endothelial elements. The spleen shows no apparent change.

Case 5. A married woman of 35, with one child aged 3, was admitted to hospital on 1.9.24. She had always been dark. In 1919 she had an illness lasting three months, in which she felt weak and unable to work. At the same time white patches appeared round the mouth and on the hands. Since her confinement in 1921 she had become browner, and on the whole progressively weaker, though with periodic remissions and exacerbations. In the last few months there was much vomiting. On admission she was found to be much bronzed, especially round the nipples and umbilicus, on the front of the knees and elbows, and on

the face. There were leucodermic patches round the mouth and on the hands. Blood-pressure 82/64. No abnormality was found in the alimentary, respiratory, nervous, and genito-urinary systems. She was treated by injections of adrenalin and extract of whole suprarenal by the mouth, but did not improve. She was found dead in bed in the night of 12.9.24. At autopsy pigmentation was found in the areas described. The heart showed brown atrophy and weighed only 150 grm. The other organs showed general atrophy. In spite of prolonged search no trace of suprarenal tissue was found. There was present at the upper pole of the right kidney a piece of pigmented fat. Microscopical examination of this showed no trace of suprarenal tissue.

The first three cases are very similar. In all the medulla was present in normal amount and appeared normal apart from minor changes in Case 3. The cortex in all was greatly diminished, and consisted of small islands of greatly enlarged hyperplastic cells undergoing a highly characteristic form of degeneration. Minor differences were present, such as the haemorrhage in Case 2 and the fibrous strands separating the cortical islands in Case 3, but the general similarity is so marked that all the sections might have come from the same block. In the case of the right suprarenal of Case 2 the process has gone on to almost complete destruction of the cortex, leaving the medulla practically normal. This is also the case with both main suprarenals in Case 4, in which the few remaining bloated cortical cells show that the process is essentially identical with that in the other three; but in this case the medulla showed several areas of dense round-cell infiltration, though most of it was normal. The accessory suprarenal beneath the capsule of the right kidney was originally, judging from its position, of the cortical type, but it had undergone complete destruction apart from a few isolated bloated hyperplastic cells. In Case 5 it is inconceivable that the patient had actually lived without suprarenals. It is much more likely that the glands were so atrophied as to escape detection. How easy this is is shown by the fact that in Case 4 the main suprarenals were not found until the tissue in which they lay was examined microscopically.

Suprarenal atrophy is a not uncommon cause of Addison's disease. Among cases published recently Connybeare and Millis (20) found 7 cases of atrophy among 29 post-mortems on cases of Addison's disease; Harbitz (34) found 2 cases among 22 post-mortems; Rowntree (71) found 1 case in 9 post-mortems; while among 8 post-mortems at the Queen's Hospital during the last nine years there have been 3 cases of atrophy. This makes 13 cases of atrophy out of 68 cases of Addison's disease, or 19 per cent. All the others were examples of fibro-caseous tuberculosis.

Many other cases of Addison's disease with suprarenal atrophy have been described, and 42 of the more recent ones are set out in the table, pp. 138–42. These with the 5 reported above make 47 all told. The age and sex are stated in 38. The age varied from 10 to 53, the average being 35, and the proportion of males to females is 20 : 23. Lewin (54) says that the proportion in Addison's disease in general is 3 : 2, while Rolleston (68) says it is 8 : 9.

In the table the cases are divided into four groups. In Group A there are 18 cases with a marked lesion of the cortex, usually closely resembling that in the first four cases described above, and a relatively intact medulla. The greater part of the cortex was destroyed, and that which remained consisted of islands of very large cells undergoing destruction. Varying degrees of fibrosis, round-cell infiltration, &c., were present. In Group B there are eight cases in which the medulla was normal or showed only a little round-cell infiltration and sometimes changes in its blood-vessels, while the cortex was quite absent. In Group C there are eight cases in which there was grave damage to the medulla as well as of the cortex, with much round-cell infiltration and varying degrees of fibrosis. In some cases there was the characteristic hypertrophy of the remaining cortical cells. Group D consists of eight cases in which one or both suprarenals was missing or replaced by a mass of fat or fibrous tissue. Case 5 described above belongs to this group. In one of the unilateral cases, that of Arnett, the remaining gland shows cortical changes reminiscent of those in Group A, while in another, that of Wakefield and Smith, the remaining gland showed no cortex but only some diseased medullary tissue.

It seems probable that all these cases represent stages in a similar pathological process. There is first, as in the first four cases described above and the cases in Group A, a destruction of the greater part of the cortex, leaving the medulla intact. Regeneration of the remaining cortical cells results in the formation of islands of hypertrophied cells, which in turn degenerate by a process of progressive vacuolation. In some cases, as in Case 4 and the right gland in Case 2, the process goes on till the cortex is practically destroyed, while the medulla is still fairly normal. In other cases (Group C) the medulla is attacked while there is still some cortex left. Finally, as in Case 5 and Group D, the suprarenals (one or both) are completely destroyed. Case 4, in which the accessory cortical suprarenal was practically converted into a mass of fibrous tissue, and the cases of Arnett and Wakefield and Smith, mentioned above, form connecting links with the more usual type of case. In the bilateral cases perhaps the suprarenal function was partly carried on by small accessory suprarenals which were not able completely to compensate for the loss of the main glands. A case bearing on this point has been described by Schnyder (75). A man of 68 with a pigmented skin died of carcinoma of the larynx. Twenty-four years before he had been in hospital with a diagnosis of Addison's disease, but had recovered. At post-mortem his right suprarenal could not be found, but the left was hyperplastic, weighing 11 grm., the normal weight of both glands together.

The process seems to be similar in all cases, but some authors have thought it to be of inflammatory, others of atrophic origin.

There are three possibilities as to the nature of the process:

1. That it is a congenital hypoplasia of the glands, according to Neusser and Wiesel (65), especially of the chromaffin system, and associated, as Hart (36) thinks, with status thymico-lymphaticus. This view seems to be untenable.

The process first attacks the cortex, not the medulla or the chromaffin system. The thickening of the capsule, increase in fibrous tissue, and round-cell infiltration are all in favour of an acquired, not a congenital process. Moreover, in many cases the stages of the actual destruction of the cortical cells, with areas of regeneration and hyperplasia, are clearly visible. For these reasons it may be concluded that the atrophy is not due to congenital hypoplasia.

2. That the atrophy is due to chronic inflammation. Simmonds (79) says that tuberculosis is the commonest cause of atrophy, and that the tuberculous process may heal so completely that it is impossible to find the cause of the fibrosis. But in most cases of suprarenal atrophy there is no tuberculosis elsewhere in the body, or, as in Case 1, there is only an old healed lesion at the apex of a lung. This does not absolutely disprove the tuberculous origin of the disease, since in frank caseous suprarenal tuberculosis there may be no obvious primary tuberculous focus elsewhere in the body. Simmonds also considered the possibility of a syphilitic origin of the atrophy. Syphilitic lesions elsewhere in the body had previously been mentioned in only two cases, including Barlow's (6), in which there was a gumma of the kidney. In the few recorded cases of syphilitic Addison's disease the changes in the suprarenals are different from those in ordinary cases of atrophy. Jacquet and Sezary (44) have described a case in a man of 66. The suprarenals were larger instead of smaller than normal, the capsule was thickened, the fibrous stroma increased, and there were many foci of lymphoid infiltration. Spirochaetes were present in large numbers. The medulla was normal. Simmonds (80) says that though spirochaetes are commonly found in the suprarenals of congenitally syphilitic children, gross anatomical changes were found in only 18 out of large numbers examined. Gummata were present in 1 (Aschoff (3) had previously described 3 cases of congenital suprarenal syphilis with gummata), necrotic areas in 4, and more or less widespread inflammatory infiltration of the parenchyma in 4. In all the 18 there was inflammation and thickening of the capsule with round-cell infiltration. The changes extended into the outer layers of the cortex, the cells of which were often atrophic. Simmonds thought that the healing of such a process might easily produce the picture of suprarenal atrophy. In his two cases of atrophy (79) there was no syphilitic history and no syphilitic changes in the organs, but the suprarenals showed endophlebitis and endarteritis of their vessels, changes which he thought suggestive of syphilis. In three of the cases of Fahr and Reiche (Group A) there were similar changes in the walls of the veins, but in only one of these was there a history of syphilis, and even in this case the Wassermann reaction was negative. In the great majority of cases described by other authors, and in the cases described above, no such changes in the vessels were present. It is possible that the vascular changes are the result of the atrophy, and that they have no etiological significance. There is thus no adequate evidence for the syphilitic origin of the suprarenal atrophy.

There remains the possibility that the process may be a chronic simple inflammation, though very little is known of such conditions. In cases of chronic

inflammation in the neighbourhood of the suprarenals the capsule may be thickened and the cortex fibrosed, but such changes are confined to the surface. It is thus improbable that the process is a chronic simple inflammation of the suprarenal.

Sometimes suprarenal fibrosis results from trauma. Borrmann (15) describes a case in a man who four years before death was struck in the side, with fracture of a rib. Symptoms of Addison's disease followed at once. The suprarenals were found to be greatly enlarged, fibrous, and adherent to the surrounding structures. They consisted of dense fibrous tissue infiltrated with lymphocytes and showed much old blood pigment with a few cells representing the remnants of the gland parenchyma. No comparison can be drawn between such cases and the usual types of suprarenal atrophy.

3. That the process is a simple atrophy of the cortex (and later of the medulla too) with attempts at regeneration. The cause is obscure. As Beitzke (7) points out, the usual causes of atrophy, such as disuse, over-use, pressure, neurotrophic disturbance, and circulatory lesions, can rarely be shown to have acted in cases of suprarenal atrophy. Nevertheless, it is possible that over-use may be a contributory cause. Jaffe (48) found that if, in rats, excessive work is thrown on the accessory cortical suprarenals by the removal of the main glands, such rats often die after months of ill health, and the accessory suprarenals show 'interstitial fibrosis, vacuolation and distortion of the cells and giant cells'. This description recalls the appearances in cases of human cortical suprarenal atrophy, and suggests the possibility that the changes may in part be due to exhaustion atrophy of a cortex previously deficient owing to some other cause.

Again, in a few cases, such as those of Simmonds (Group B) and Fahr and Reiche (Group A), there were lesions in the suprarenal vessels, but it is more likely that they were due to the same cause as the atrophy, or were due to the atrophy, rather than that they caused the atrophy. Many cases of severe vascular lesions of the suprarenals have been described. Hirsch and Capps (40) describe a case of thrombosis of the suprarenal veins, resulting in death in six weeks. Areas of necrosis of cortical cells were present, and the medullary cells were shrunken and pyknotic. Similar cases have been described by Straub (82), Weisenfeldt (86), Ellis (27), Schönig (76), Crowe (22), Arnaud (1), Bittorf (10, 12), Hornowski (41), and others. In most cases there were areas of necrosis and haemorrhage, especially in the cortex. In Scott's case (78) the lesion was confined to the cortex. But in none of these cases had the process lasted long enough for chronic changes to occur. Karakascheff has described a case of old suprarenal haemorrhage in a child who died of diarrhoea, with no symptoms of Addison's disease. There were old organized haemorrhages destroying the medulla of both suprarenals, but leaving much normal cortex. Henschen (38) describes a case in which one suprarenal was converted into a large blood cyst. The pathological process in all these cases is quite different from that in the cases of atrophy, but in a few cases the changes show some resemblance to those in atrophy. Thus Veit (83) describes a case of Addison's disease in which one

suprarenal was absent and the vein of the other was thrombosed. The medulla was necrotic and the cortex showed areas of necrosis, fibrosis, and atrophy, with other areas in which the cells were enlarged. Furuta (30) describes a case of infective endocarditis with many emboli in branches of the suprarenal arteries The medulla was normal. The cortex showed fibrosis, round-cell infiltration, much necrosis and atrophy of the parenchymal cells, and small adenoma-like areas of regeneration. Such changes as these might conceivably represent the first stage of suprarenal atrophy, but, since there were no vascular changes in most of the cases of atrophy described, it is improbable that this is true in most cases.

Bloch (13), who thinks that the symptoms of Addison's disease are due to lack of adrenalin, suggests that the round cells present in atrophic suprarenals are not lymphocytes but sympathicogonia which have proliferated in order to compensate for the lack of adrenalin, and have thus caused atrophy of the cortex. But the cells have neither the appearance nor the arrangement typical of sympathicogonia, and they have been identified by Paunz (67) as derivatives of the reticulo-endothelial system. They are often confined to the cortex, the medulla being free from them. Bloch's suggestion is therefore not warranted. None of the theories put forward give a satisfactory explanation of these cases of suprarenal 'atrophy'. It seems there is a slow necrosis of the cortex with destruction of most of the cells. Those which remain undergo compensatory hypertrophy and multiply to form adenoma-like nodules, the cells of which are then attacked by the same process; or perhaps part of the further degeneration is due to exhaustion atrophy of the remnants of cortex. The process may later spread to the medulla. The fact that the process primarily involves the cortex of both suprarenals and, as in Case 4, any accessory cortical tissue which may be present suggests that a toxin with a special affinity for suprarenal cortex may be at work. It is possible that the toxin may be of bacterial origin. Aschoff (4) says that in diphtheria and scarlatina the medulla is practically normal, while the cortex shows oedema and loss of lipoid. In other severe infections the cortex shows oedema, loss of lipoid, and vacuolation and even necrosis of its cells, with an increase in vascular connective tissue. Since few people go through life without having a severe infection of some sort, it is possible that one of these may be the prime cause of the atrophy, but there is no definite evidence as to this. Neither is there any evidence that the cause is a poison produced by faulty metabolism. The cause is really quite unknown.

In many cases of Addison's disease due to various lesions of the suprarenals other endocrine glands are also diseased. In the literature most attention is concentrated on the thymus and lymphoid tissues. Many cases of enlargement of the thymus and lymph glands have been described in Addison's disease, due both to atrophy and to tuberculosis of the suprarenals. Thus Hedinger (37) describes fifteen cases of Addison's disease, one with atrophy, the others with tuberculosis of the suprarenals. In seven of these, including the case with suprarenal atrophy, there was a status thymico-lymphaticus, and in another five there was a generalized lymph-gland hyperplasia. But such cases have not been

recorded so frequently by most authors. In Case 4, described above, remnants of thymus were present, and there was a slight generalized lymph-gland hyperplasia, but in the other four cases no such changes were seen. The significance of these changes is doubtful. It has been suggested that they are due to the action of the tuberculous toxin, but, as a similar hyperplasia occurs in cases of atrophy, this is untenable. However, if it is held that the atrophy is due to the action of a toxin, the lymphoid hyperplasia might be due to the same toxin. Some authors, such as Neusser and Wiesel (65), Hart (36), and others, attach great importance to this thymic and lymphoid hyperplasia in Addison's disease, and think it intimately associated with hypoplasia of the chromaffin system, which they consider an essential factor in the production of Addison's disease. Others, such as Jaffe (45, 46, 47) and Marine, Manley, and Baumann (61), think that the thymic hyperplasia is associated with impaired function of the suprarenal cortex, and bring forward experimental evidence in support of this.

The thyroid gland is also often diseased in Addison's disease, due both to atrophy and to tuberculosis of the suprarenals. In most of the cases described there was some infiltration with lymphocytes and fibrosis. In some cases, as in Case 1 described above and Schmidt's cases (74), the lymphoid infiltration was very dense. In addition, the gland parenchyma often showed changes, either of diminished or of increased activity. In Case 1 the changes were as severe as are met with in many cases of myxoedema, yet neither in this case nor in many others described were there any symptoms of deranged thyroid function. In some cases, however, both of atrophy (as in Rössle's case (70) and in Case 4) and of tuberculosis (Elsner (28) and Löffler (55)), the symptoms and pathological changes of Graves' disease as well as of Addison's disease were present, while in other cases there were also symptoms of myxoedema. It seems probable that the changes in the thyroid are due to the same cause as the suprarenal lesion, and not to loss of suprarenal function.

The pituitary is less frequently and usually less severely affected. In some cases, as in Cases 1 and 3 and in Hewer's (39) case of suprarenal tuberculosis, there is marked predominance of eosinophil cells in the anterior lobe, while in Case 4 there was marked predominance of basophil cells. This type of change might well be related to changes in the suprarenal function.

Changes in the genital organs may occur, but in cases of clinically pure Addison's disease are usually slight and do not give rise to symptoms, as in Lucksch's case (57) and Case 3, in both of which there was slight increase in the stroma of the testis with diminished spermatogenesis.

Occasionally the pancreas is involved, as in Arnett's case of suprarenal atrophy (2), in which there were symptoms of diabetes as well as of Addison's disease.

It thus seems that it is not uncommon to find one or more of the other endocrine glands affected in cases of Addison's disease, especially those due to suprarenal atrophy.

In most cases of Addison's disease, especially those due to tuberculosis, both

the cortex and the medulla are destroyed. It is, therefore, natural that many clinicians and pathologists, familiar as they are with the striking pharmacological properties of adrenalin, should assume that most of the symptoms are due to the destruction of the medulla and the chromaffin system in general, in spite of the fact that the whole trend of the recent physiological evidence is to show that the minute amount of adrenalin naturally produced in the body can at the most only help in the production of certain emotional reactions, and that its complete absence causes no apparent ill health in animals, while the cortex is essential to life. Thus Langdon Brown says (17): 'Addison's disease is essentially due to absence of adrenalin from the circulation. If the sympathetic cannot act in the absence of adrenalin, the cardinal symptoms of Addison's disease are explained. As the sympathetic supplies accelerator fibres to the heart and constrictor fibres to the blood-vessels, their paralysis must result in cardio-vascular atony. The sympathetic also supplies the stomach with inhibitory fibres; their paralysis leads to motor irritability of the stomach and therefore to vomiting. The effects of adrenalin in maintaining the tone of voluntary muscle explains another factor in the profound asthenia. The pigmentation probably results from the relaxed condition of the blood-vessels, like that after poulticing or exposure to light.' He further says (18) that 'progeria, the premature senility of children, . . . is the only condition which has been associated with defect of the suprarenal cortex'. Essentially similar views are expressed in most of the standard text-books of medicine and pathology. But very few cases of Addison's disease with a pure medullary lesion have been described, and these seem doubtful. Thus in Banwart's case (90) of extensive abdominal malignant disease with secondary deposits destroying the medulla but leaving most of the cortex intact, there were symptoms suggesting Addison's disease except that the blood-pressure was normal. But vomiting, asthenia, and even pigmentation might be expected with extensive abdominal malignant disease even without involvement of the suprarenals, so that this case is inconclusive.

Again, many cases of Addison's disease with tuberculosis of the suprarenals have been described in which the medulla was quite destroyed but small parts of the cortex were normal (Eidelsberg (26), Mackenzie (58), Kahn (48), Loeffler (55)); but in all cases the remnant of normal cortex was evidently insufficient to support life. Bornstein and Gremels (14) have shown that at least one-quarter of the suprarenal cortex must remain if life is to continue.

On the other hand, Karakascheff (51) describes the case of a child of 5 months who died of diarrhoea with no symptoms of Addison's disease, though the medulla of both suprarenals was destroyed by old haemorrhage. He also (51) compares two cases of tuberculosis of the suprarenals. In both the medulla was destroyed and only a few islands of normal cortex were left. In one the solar plexus contained chromaffin cells, but no accessory cortical suprarenals were found. This patient died of Addison's disease. In the other, there were no chromaffin cells in the sympathetic, but there was a large accessory cortical

suprarenal. There were no symptoms of Addison's disease. Marchand (59) and Schmidt (73) describe cases in which the suprarenals were destroyed by tuberculosis, but large accessory cortical suprarenals were present and no symptoms of Addison's disease. In Schmidt's case there were no chromaffin cells in the sympathetic. In many cases of Addison's disease with suprarenal atrophy, as in the first four cases described above, and those in Groups A and B of the table, the lesion is practically confined to the cortex, the medulla being normal. Also, in those rare cases of amyloid disease of the suprarenal in which the lesion is severe enough to cause Addison's disease, the lesion is practically confined to the cortex, where the parenchymal cells are destroyed by the pressure of the amyloid material, while in the medulla the amyloid material is confined to the walls of the blood-vessels, and the parenchymal cells are normal and often show a good chromaffin reaction. Such cases have been described by Hunter and Rush (42), McCutcheon (63), Schlesinger (72), and Bittorf (12), while in Schultz's case (77) both the cortex and the medulla were destroyed.

Secondary deposits of growth, though quite commonly found in the suprarenals, only rarely cause Addison's disease. This seems to be due to the fact that such deposits are usually present in the medulla or in the peri-suprarenal fat. But Bittorf (12) describes a case in which secondary deposits from a hypernephroma destroyed the cortex, while leaving the medulla relatively and the extra-suprarenal chromaffin tissue completely intact. Symptoms of Addison's disease were present.

The results of treatment do not throw much light on the subject. Extract of cortex and injections of even large doses of adrenalin are usually disappointing. Cures have been reported as the result of transplanting suprarenals, e. g. by Currie (23) and Dmitrijew (24), but little importance can be attached to cases without autopsy. Thus Hurst (43) describes a case in which much improvement occurred after a foetal suprarenal had been grafted into the testicle. The patient died two years later, and was found to have cirrhosis of the liver. The suprarenals were normal and the graft had been converted into fibrous tissue.

The work of Wiesel on the importance of the extra-suprarenal chromaffin system is widely quoted. He says that in cases of Addison's disease with suprarenal tuberculosis the chromaffin cells in the suprarenal and sympathetic are much reduced or missing, while in cases of suprarenal tuberculosis without Addison's disease many chromaffin cells are present in the sympathetic. But in the case which he uses to illustrate this point, there were two normal accessory cortical suprarenals as well as a small remnant of cortical tissue in the main glands. He then (89) describes three cases in which the suprarenal medulla was absent or much reduced, and very few if any chromaffin cells were present in the sympathetic, while the cortex was normal. None of these cases had symptoms of Addison's disease, so that pure chromaffin hypoplasia may exist without Addison's disease. On the other hand, in many cases of Addison's disease with suprarenal atrophy (see table), tuberculosis (Karakascheff (50)),

amyloid disease (Bittorf (12)), and growth (Bittorf (12)), the chromaffin reaction is normal. Biedl (8) says that the chromaffin reaction disappears in twelve to thirty hours after death, and in many cases in which it is reported as being absent the autopsy was done longer after death than this. Wiesel himself (65) says that he meant the statement that chromaffin hypoplasia was the primary event in Addison's disease chiefly in the anatomical sense ; chromaffin hypoplasia predisposes to suprarenal tuberculosis, which attacks the medulla first, but the severe and fatal symptoms of the disease are due to the later involvement of the cortex. It thus seems that the statements so frequently made in the text-books of pathology and medicine as to the importance of the chromaffin system in Addison's disease are based on a misconception of Wiesel's views.

Examination of the pathological evidence thus shows that the symptoms of Addison's disease occur only when the cortex is severely damaged, and that all the symptoms may occur when the lesion is confined to the cortex, leaving the medulla, the sympathetic, and the extra-suprarenal chromaffin system apparently normal. On the other hand, the chromaffin system may be extremely hypoplastic without there being any symptoms of Addison's disease. The pathological evidence, therefore, agrees with the physiological evidence as to the importance of the cortex and the relative unimportance of the chromaffin system and of adrenalin. It seems, then, reasonable to assume that the symptoms of Addison's disease are due to deficient function of the suprarenal cortex.

Summary and Conclusions.

1. Five cases of Addison's disease are described. In four of them there was a peculiar and characteristic lesion of the cortex, with destruction of most of it. The medulla was little or not at all damaged. In the fifth case no suprarenals were found. It is suggested that this may represent the end stage of the process illustrated by the other four cases.

2. The recent literature is reviewed and several similar cases are briefly described and tabulated.

3. The cause of the process is discussed. No definite conclusions are possible, but it is suggested that the process is a necrosis of cortical cells caused by some unknown toxin which has a special affinity for them. This is followed by focal regeneration, with the production of hyperplastic islands of hypertrophied cells, which are then attacked by the same process. The few cortical cells left after the primary damage are probably overworked, and it is possible that part of the subsequent degeneration is due to this.

4. In many cases of Addison's disease due to suprarenal atrophy or tuberculosis other endocrine glands are also diseased. In Case 1 the lesion of the thyroid was almost as marked as that of the suprarenals, though there were no symptoms of thyroid disease. In Case 3 there were mild symptomless lesions of the thyroid and testis. In Case 4 there were symptoms and pathological

changes of Graves' disease as well as of Addison's disease. In the other two cases the other endocrine glands were not examined.

5. The pathological evidence as to the relative importance of the cortex and medulla is reviewed. It is shown that the symptoms of Addison's disease occur only when most of the cortex is destroyed, and that they occur then even if the medulla and the chromaffin system are normal. On the other hand, the chromaffin system may be practically absent, and if the cortex is normal there are no symptoms of Addison's disease. The inference is drawn that the symptoms are due to disease of the suprarenal cortex and not to disease of the medulla or of the chromaffin system as a whole.

I wish to express my great indebtedness to Dr. L. G. J. Mackey, Prof. L. Ball, and Dr. J. G. Emanuel for permission to publish Cases 1, 4, and 5, admitted under their care; to Dr. R. G. Abrahams and Dr. F. L. Lamb for giving me access to the sections and case notes of Cases 2 and 3; to Prof. G. Haswell Wilson and Dr. J. F. Brailsford for help with the microphotographs; and to Prof. Haswell Wilson for his valuable criticism and help throughout.

TABLE.

Group A.

No.	Author.	Age.	Sex.	Cortex.	Medulla.	Sympathetic and Chromaffin System.	Remarks.
50	Karakascheff	41	M.	Capsule thickened and for most part lay directly on medulla. A few islands of cortex left, with greatly enlarged cells with large poorly stained nuclei. Cytoplasm vacuolated. Many foci of round-cell infiltration	Very well preserved. Less round-cell infiltration than in cortex. Granules of iron pigment present.	—	—
70	Rössle	40	F.	Suprarenals weighed together less than 6 grm. In many places whole cortex had disappeared, while in some places there were small areas of regeneration. Small round-cell infiltration and haemorrhage	Medulla normal, apart from some round-cell infiltration	—	Process considered to be an inflammatory atrophy, especially of the cortex
57	Lucksch	34	M.	Cortex consists of many small adenoma-like nodules separated by fibrous septa. There are also some larger masses of cortex. Cells mostly abnormal, and most much bigger than normal. From one-fourth to one-fifth of the scanty cortical cells showed no nuclear staining and were therefore judged to be necrotic. Nuclei of some of the other cells were greatly enlarged, and others pyknotic. Cytoplasm of some showed normal fine vacuolation, others were homogeneous, and many showed large vacuoles. Fat content diminished and was not of the normal doubly refractile variety. Much small-cell infiltration	Normal, apart from a little round-cell infiltration	Chromaffin reaction in medulla negative	Process thought to be inflammatory atrophy, especially of the cortex
29	Fahr and Reiche	34	F.	Cortex much reduced and to a large extent replaced by fibrous tissue showing infiltration with round cells and blood. A few small hyperplastic islands of cortex present. Cells large and not vacuolated. Nuclei large	Well preserved. Walls of veins infiltrated with round cells	Chromaffin reaction normal	Thought to be an inflammatory atrophy
		26	M.	Similar changes	Similar	—	Syphilis three years before. Wassermann negative

		46	F.	Similar changes	Similar	Coeliac ganglion normal except for a little round-cell infiltration	—
		25	F.	Similar changes	Similar. Veins normal	—	—
		22	M.	Similar changes	Similar. Veins normal	Coeliac ganglion normal	—
		?	M.	Similar changes	Similar. Veins normal	—	Brother of last case
13	Bloch	29	M.	Practically destroyed—represented by few groups of cells which could be seen undergoing destruction. Foci of round-cell infiltration	Many foci of round-cell infiltration	Chromaffin reaction in medulla normal	—
81	Steinbiss	52	F.	Capsule thickened, and fibrous strands from it cut up cortex. Only portions of the zona fasciculata persist, and in some places capsule lay directly on medulla. Cortical cells greatly enlarged, up to ten times normal diameter. Often contained up to five vesicular nuclei. Process of degeneration by increasing size of vacuoles well marked, resulting finally in disappearance of cells.	Slightly reduced in amount and shows a little round-cell infiltration, but otherwise normal	—	Thought to be a slow non-inflammatory degeneration
62	Matras	44	F.	Cortex practically absent, though it shows a few areas of compensatory hyperplasia. Foci of round-cell infiltration	Normal except for a little round-cell infiltration	—	—
		36	F.	Similar changes	Similar	—	—
37	Hedinger	49	M.	Only a very small amount of cortex recognizable. Foci of round-cell infiltration	Well preserved. Foci of round-cell infiltration.	No chromaffin reaction in medulla	P.M. 43 hours after death
60	Maresch	33	F.	Capsule thickened. Cortex greatly thinned, being at the maximum 1 mm. thick, and arrangement into three zones recognizable only here and there	Normal in amount and appearance	Normal chromaffin reaction	—
78	Scott	17	F.	Cortex practically disappeared. Much round-cell infiltration and congestion. Capsule thickened	Intact except for some round-cell infiltration	—	—
74	Schmidt	50	F.	Capsule thickened. Cortex replaced by fibrous tissue containing an occasional and usually atrophic cortical cell. Much round-cell infiltration	Normal except for some round-cell infiltration	No chromaffin reaction in medulla	P.M. more than 24 hours after death

TABLE (*continued*).

No.	Author.	Age.	Sex.	Cortex.	Medulla.	Sympathetic and Chromaffin System.	Remarks.
32	Gougerot and Gy	52	M.	Suprarenals slightly diminished in size. Capsule much thickened. Much increase in fibrous tissue with great atrophy of cortical cells, which were present in small groups of not more than twenty cells embedded in fibrous tissue	Medulla practically normal	—	Perhaps not of same nature as other cases
				Group B.			
33	Hansemann	—	—	Suprarenals normal in length and breadth, but very thin. No trace of cortex	—	—	No certain evidence of inflammation
79	Simmonds	41	F.	Replaced by fibrous tissue rich in blood-vessels and showing many foci of round-cell infiltration.	Much medulla left, showing great round-cell infiltration. Vessels showed thickening of media and intima, with obliteration of lumen in some cases	Nests of ganglion cells in medulla	Possibility of syphilitic origin suggested
66	Obendorfer	—	—	Cortex completely destroyed	Normal	Good chromaffin reaction in medulla	—
31	Goldschmidt	36	F.	Destroyed	Much of medulla normal	Good chromaffin reaction in medulla and solar plexus	
81	Wells	—	—	'Selective destruction of cortex'	Normal	—	—
74	Schmidt	38	F.	No cortex present at all	In fair amount and normal, apart from some round-cell infiltration	—	Regarded as simple atrophy
52	Lange	50	F.	Atrophied	Relatively intact	—	Regarded as simple atrophy
56	Löwy	21	M.	Capsule thickened. Cortex absent. Much round-cell infiltration	Normal	—	—

Group C.

69	Roloff	22	M.	L. suprarenal shows islands of cortical tissue only here and there. R. shows only occasional remnants of parenchyma. Small round-cell infiltration in both	L. shows well-preserved medulla. R. shows very little either of cortex or medulla	—	Cortex and medulla regarded as equally affected
53	Langerhans	53	F.	Zonae glomerulosa and reticulata missing. Z. fasciculata still recognizable in places. Small areas of compensatory hypertrophy. Vessels engorged. Much round-cell infiltration	Fatty change and round-cell infiltration	—	Round-cell infiltration regarded as reparatory in function
79	Simmonds	27	M.	Cortex replaced by narrow strand of fibrous tissue rich in elastic tissue and round and spindle cells. Groups of large very swollen-looking cells are described. Uncertain from the description whether these are cortical or medullary, but their description reads very like that of the large hypertrophied cells of the cortex in Cases 1, 2, and 3 described above	So thickly infiltrated with round cells that structure recognizable only here and there	Groups of ganglion cells in medulla	—
50	Karakascheff	39	F.	Only a few parenchymatous cells of doubtful nature left. These resemble cortex rather more than medulla	None recognizable	—	—
64	Medlar	28	M.	Atrophy of cortex with large areas in which there was no parenchyma. Marked fibrosis and extensive round-cell infiltration	Marked fibrosis and round-cell infiltration	—	—
		29	F.	Suprarenals not recognizable by naked eye, but microscopically showed small clumps of 'cortical or medullary tissue'. Some of the cells were necrotic and infiltrated with mono- and poly-nuclear cells. Much round-cell infiltration. Many of the remaining cortical cells much hypertrophied	—	—	—
84	Wakefield and Smith	35	M.	Capsule much thickened. Cortex had 'lost its characteristic structure; the cells varied in size, some containing large vacuoles'. Much round-cell infiltration. The suprarenals were very small and thin and embedded in fat	No medulla identified	Summarized as 'destructive caseous lesion', though in the detailed description no mention of caseation or of any T. B. lesion except old healed focus in lung	—

TABLE (*continued*).

No.	Author.	Age.	Sex.	Cortex.	Medulla.	Sympathetic and Chromaffin System.	Remarks.
25	Donath and Lampl	24	F.	Suprarenals very small. Here and there a few normal-looking cortical cells, but arrangement much disturbed. Much fibrillar connective tissue and round-cell infiltration	None present. Replaced by round cells and connective tissue	—	—
				Group D.			
21	Coupland	34	M.	R. suprarenal replaced by a mass of pigmented fat. L. about a third the normal size	—	—	—
54	Monti, quoted by Lewin	10	M.	One suprarenal absent. Other much reduced in size	—	—	—
16	Bramwell	36	M.	Suprarenals reduced to small masses of fibrous tissue	—	—	—
16	Bramwell	47	M.	Suprarenals replaced by masses of pigmented fat	—	Atrophy of semi-lunar ganglia	—
85	Warthin	40	M.	Absence of all trace of adrenal tissue on microscopic examination	—	—	—
20	Connybeare and Millis	—	—	In one case out of seven of atrophy of the suprarenals mentioned, neither suprarenal could be found	—	—	—
2	Arnett	39	F.	R. suprarenal not found. L. much smaller than normal. Great increase in connective tissue and round-cell infiltration. Cortical cells mostly small and devoid of lipoid, but at periphery are islands of large cells also devoid of lipoid	—	—	—
84	Wakefield and Smith	28	M.	R. suprarenal converted into knot of fibrous tissue with round-cell infiltration, and was supplied by sclerosed obliterated vessels. L. suprarenal small and flattened. Capsule thickened and infiltrated with lymphocytes. No cortex recognized. Much congestion, some fibrosis, and infiltration with round cells	Some medullary substance present. Much fibrosis, round-cell infiltration, congestion, and haemorrhage	—	—

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FIG. 2. Suprarenal from Case 2. ×100. The junction between cortical and medullary tissue is shown. The cortex (upper and left portion of the field) consists of large bloated-looking cells, many of them with large hyperchromatic nuclei. They are very loosely and irregularly arranged, and many spaces formed by the disappearance of cells are present. The medulla (lower and right portion of the field) appears normal.

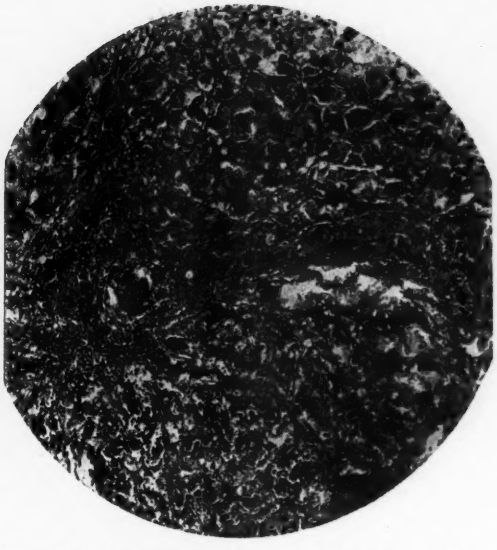


FIG. 3. From the suprarenal of Case 2. ×100. Shows similar features in the cortex (above) and medulla (below). In addition there is a strand of dense fibrous tissue in the cortex and separating the cortex from the medulla. This fibrous tissue shows round-cell infiltration.



FIG. 4. Suprarenal from Case 3. ×100. Shows a few groups of the typical large bloated cortical cells embedded in dense fibrous tissue showing some round-cell infiltration.

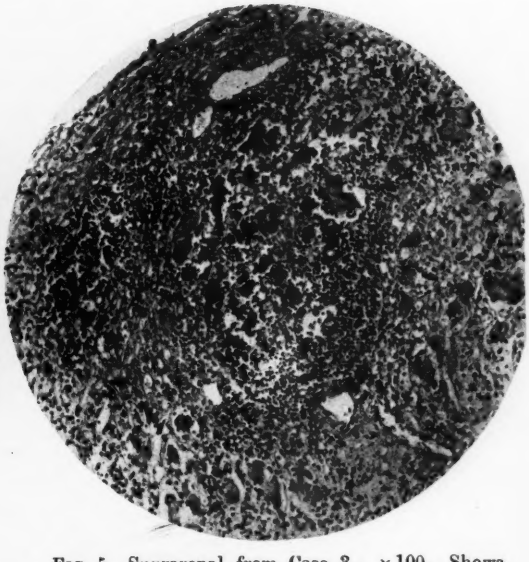


FIG. 5. Suprarenal from Case 3. ×100. Shows groups of similar cortical cells embedded in fibrous tissues showing dense round-cell infiltration. The capsule is thickened.

FURTHER NOTES ON THE SEDIMENTATION-RATE OF ERYTHROCYTES[1]

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In a previous paper by one of us (H. B. N.) (1) on the sedimentation-rate of erythrocytes in certain tropical diseases certain conclusions were drawn as a result of the investigations there detailed, and it was suggested that increased rapidity of sedimentation was associated with some concomitant derangement of the liver, and further, that probably the phenomenon of rapid sedimentation was due to a combination of both physical and chemical changes.

In an attempt to elucidate the causation, a further series of cases has been investigated. This series consists of twenty-five cases, most of which were suffering from tropical diseases.

List of Cases: Condition at Date of Investigation.

No. 1. Sprue. M. Chronic case with relapses. Diarrhoea controlled just prior to observation. Milk diet. Liver soup not added till later.

No. 2. Sprue. M. Acute case with diarrhoea and icteroid complexion.

No. 10. Sprue. M. Chronic sprue: previous history includes cholera, and consumption of alcohol very high.

No. 15. Sprue. M. Two years' history of sprue. Febrile. Treated with liver preparation (Armour's). Gaining weight.

No. 17. Sprue. M. (*a*) Ill for seven years. Afebrile. Started on milk diet. Stools very loose. (*b*) Stools better. Liver diet started a few days before the observation was made. (*c*) Just prior to discharge—greatly improved. Had gained over three stone in weight in past three and a half months.

No. 20. Sprue. M. Very ill. Almost incontinent with diarrhoea. Milk diet. Liver soup added later and great improvement has followed.

No. 22. Sprue. F. Afebrile. An old case of sprue, readmitted for observation: no signs of active sprue now.

No. 3. Kala Azar. M. Moderately severe case. Liver puncture showed parasites. Moderate degree of anaemia.

No. 13. Kala Azar. M. Case well treated with Stibamine glucoside. Afebrile for five weeks: has put on 18 lb. in weight during that time.

No. 14. Kala Azar. M. (*a*) Recently febrile with very mild infection: K.A. fever had subsided a fortnight before: on Stibamine glucoside and quinine. (*b*) Improving—no fever. (*c*) Stibamine glucoside course finished: greatly improved.

[1] Received July 27, 1928.

No. 16. Kala Azar. M. (*a*) Case first diagnosed and treated in Calcutta eight months before. On admission here spleen puncture showed parasites. Had lost over 2 stone in weight. Febrile. Treatment not yet restarted. (*b*) Has had further treatment with Stibamine glucoside. About to be discharged. Has gained over 1 stone in weight. (*c*) Readmitted—relapse—more Stibamine given —low fever—weight as when last discharged. (*d*) About to be re-discharged—improved.

No. 7. Malaria. M. Subtertian 'ring forms' in blood. On quinine treatment: febrile up to day before observation.

No. 8. Malaria. M. Subtertian 'rings' found: first exposed to malaria on west coast of Africa, six months ago. Had 'fever' ever since. Very low fever now. Treated with Tab. Plasmoquine Co.

No. 9. Malaria. M. Subtertian 'rings and crescents' in blood. No fever at time of observation. Treated with Tab. Plasmoquine Co.

No. 18. Malaria. M. Gives a history of chronic fever. No parasites found. Treated with Tab. Plasmoquine Co. Gaining weight.

No. 24. Malaria. M. Case of treated subtertian malaria. Convalescing.

No. 25. Malaria. M. Chronic malarial history. No parasites found: case complicated with boils: febrile till two days before observation. Treated with Tab. Plasmoquine Co.

No. 21. Trypanosomiasis. M. From Gambia. Febrile. Trypanosomes in peripheral blood. Tryparsamide treatment just started.

No. 6. Secondary anaemia. M. Probably due to oral sepsis. Marked general debility.

No. 12. Multilobular cirrhosis of liver. M. Barman on liner for many years. Liver irregularly large and hard. Biphasic van den Bergh reaction. Wassermann negative.

No. 5. Chronic bacillary dysentery. M. Febrile—in acute dysenteric condition. Required caecostomy later.

No. 11. Amoebic hepatitis. M. ? With abscess—under Emetine treatment.

No. 19. ? Postencephalitic condition. M. Neurasthenic: diagnosis uncertain. Admitted for observation.

No. 23. Lobar pneumonia. M. In early unresolved state. History suggestive of amoebic dysentery. Acute hepatitis also diagnosed.

No. 4. Addisonian anaemia. F. Early case admitted for observation.

Method of Numerical Comparison of Sedimentation-rates.

In previous investigations by one of us (H. B. N.) on the sedimentation-rates charts were drawn to show these rates. It occurred to us that some better method of comparing results than by means of curves might be employed.

In order to have numbers to compare instead of curves, a standard of measurement had to be devised. The technique employed, using 15 c.c. graduated centrifuge tubes as in our previous experiments, excluded the use of figures directly comparable with those of Fahraeus, who uses tubes 17 cm. × 9 mm., and with those of Linzenmeier, whose tubes are 6·5 cm. × 5 mm., and again Westergren, diluting the blood with one part sod. citrate to four of blood, used tubes 30 cm. × 2·5 mm.

Our figures indicate the number of 0·01 c.c. of clear plasma above the sedimenting cells which appear in the particular 10 min. during which the level of the cells is sinking fastest.

e.g. If the figures of the level of red cells were as follows:

0 min.	5 c.c.
10 „	4·6 c.c.
20 „	4·1 c.c.
30 „	3·8 c.c.
40 „	3·5 c.c.

The maximum rate is shown between the 10 min. and 20 min. readings, the difference in volume of clear plasma = 0·5 c.c.

∴ sedimentation-rate = 50.

In the case of normal blood, instead of considering the maximum 10 min. fall as characteristic, the mean of the first six 10 min. falls was taken. The method of taking the mean of several is inapplicable to rapidly sedimenting blood because of the retardation of sedimentation-rate due to the aggregation of red cells at the bottom of the tube. Our normal figures varied between 4 and 12 for men, with a mean of 8. Pathological bloods gave figures up to 240, many being about 40–60. Fahraeus' normal figures—adult males are ½ to 17, average 3·3—and his pathological figures range up to about 100.

This suggests that our figures are approximately 2·4 times larger than the corresponding figures by Fahraeus' technique.

Laevulose Tolerance Tests.

Technique. Blood sugar estimations, using Maclean's method, were made with the patient fasting (three hours or more). 50 grammes of laevulose in 150 c.c. water were given, and three subsequent determinations of blood sugar at half-hour intervals were made.

Twelve cases were investigated (Nos. 1, 2, 10, 3, 13, 14, 7, 8, 9, 6, 12, 11), all of these showing a greater or lesser increased rate of sedimentation above the normal, but only two of them—No. 6 (secondary anaemia) and No. 3 (Kala Azar)—showed any very definite intolerance.

	No. 6.	*No. 3.*
Fasting blood sugar	0·090 per cent.	0·109 per cent.
30 min. after laevulose	0·115 „	0·131 „
60 „ „ „	0·128 „	0·134 „
90 „ „ „	0·128 „	0·139 „

It would appear, therefore, that it does not follow that any case showing rapid sedimentation is necessarily associated with any very definite disorder of the liver in so far as measurement by the laevulose tolerance test is concerned.

Specific Gravity and Viscosity.

It was pointed out in the previous paper referred to that the phenomenon of rapid sedimentation was probably due to a combination of both physical and chemical changes, and, arguing on the basis of Stokes' law, it was inferred that a material part in the production of the phenomenon might be played by the

specific gravity of the red cells and also by the specific gravity and viscosity of the dispersion medium, i.e. the plasma.

With this idea in mind observations were made of the specific gravity of the red cells, of the viscosity and specific gravity of the plasma, and of the individual cell volume.

Specific Gravity of Red Blood Cells.

An attempt was made to estimate the specific gravity of the red cells by the method described by Reznikoff (2), in which packed red cells are tested directly by immersion in mixtures of benzoyl benzoate and cotton-seed oil of known specific gravities, but the method was unsuccessful in our hands. In the same paper Reznikoff describes the calculation of the specific gravity of the red cells from the specific gravity of the whole blood, that of the plasma, and the percentage volume of red cells, using the formula: (sp. gr. of R. B. C. × proportion of red cells) = (sp. gr. of whole blood) minus (sp. gr. plasma × proportion of plasma).

This method was adopted in our work.

The specific gravity of the whole blood and plasma was determined by weighing in specific gravity bottles, whilst the percentage volume of red cells was obtained by centrifugalizing 5 c.c. of blood to constant volume.

As an example:

	Sp. gr. of whole blood	= 1·058.
	„ „ „ plasma	= 1·027.
	Percentage volume of red cells	= 43 per cent.
Then	Sp. gr. R. B. C. × 0·43	= 1·058 − 1·027 × 0·57.
		= 1·058 − 0·585.
		= 0·473.
	∴ Sp. gr. R. B. C.	$= \frac{0{\cdot}473}{0{\cdot}43} = 1{\cdot}100.$

Using this method estimations were first made on a series of normal individuals, comprising seven men and two women. These gave figures varying from 1·094 to 1·107 with a mean of 1·098.

In eight observations on cases of sprue the values varied from 1·085 to 1·104 with a mean of 1·0982.

In seven observations on cases of Kala Azar the values varied from 1·0924 to 1·106 with a mean of 1·0985.

In ten observations on a variety of cases the values varied from 1·1085 to 1·1032 with a mean of 1·0965.

The lowest figure for specific gravity of red cells—viz. 1·085—was obtained in two cases, the one an instance of sprue with a sedimentation-rate of 50, the other a case of malaria with a sedimentation-rate of 15.

On the other hand, in two cases, one being malaria and the other Kala Azar (treated), the specific gravities were respectively 1·101 and 1·102, whilst the sedimentation-rates were found to be 55 and 20.

It would appear, therefore, that differences in the specific gravity of the red cells as estimated by us have little bearing on the sedimentation-rate.

Plasma: Specific Gravity and Relative Viscosity.

Technique. The specific gravity was estimated by careful weighing in a specific gravity bottle. The viscosity was determined in a small Ostwald viscosimeter, and the figures given express the relative viscosity of plasma compared with that of distilled water at 20° C.

In six healthy men the specific gravity of the plasma was found to vary between 1·0261 and 1·028 with a mean of 1·027.

In nine observations on cases of sprue the figures varied from 1·0205 to 1·029 with a mean of 1·0264.

In nine observations on Kala Azar the figures varied from 1·0297 (well treated) to 1·0381 with a mean of 1·0338.

In twelve observations on a variety of cases the figures varied from 1·024 to 1·0292 with a mean of 1·027.

Excluding the cases of Kala Azar, where the sedimentation-rate is very rapid and the specific gravity of the plasma abnormally high, there appears to be no marked variation in the specific gravity of the plasma to account for the increased rates of sedimentation.

In five healthy men the relative viscosity of the plasma, as defined above, varied between 1·60 and 1·64 with a mean of 1·62. In observations on cases of sprue the viscosity varied between 1·51 and 1·72 with a mean value of 1·59.

In nine observations on Kala Azar cases the viscosity varied between 1·79 (well treated) and 3·03 with a mean of 2·40. All these cases, therefore, showed high relative viscosity.

Thirteen cases of a variety of diseases gave figures varying between 1·54 and 1·97 with a mean of 1·74.

Excluding the cases of Kala Azar, where the sedimentation-rate is very rapid and the viscosity is increased to an extent not seen in any of the other conditions observed, it appears that there is no marked relationship between the viscosity of the plasma and the sedimentation-rate.

Size of Red Cells.

In a considerable number of instances the mean diameter of the fixed red cells has been worked out from an accurate measurement of 500 cells, as is done in the construction of a Price Jones curve. These measurements have all been made by one person, Miss F. M. Harvey, to whom our sincerest thanks are due.

From a consideration of the following table it will be seen that the mean diameter of the red cells varies within considerable limits, and that there would seem to be no definite correlation between size of cell and rate of sedimentation.

Sed. Rate.	M. D. of R. B. C.	Case No.	Agglutination.	Disease.
248	7·258	25	+	Malaria and sepsis.
240	7·204	23	+	Acute lobar pneumonia.
230	7·048	16 *c*	+	Kala Azar.
190	7·050	16 *d*	+	,, ,,
150	7·242	14 *a*	+	,, ,,
130	6·771	16 *b*	+	,, ,,
120	7·098	21	+	Trypanosomiasis.
62	7·004	24	not noted	Malaria.
58	8·109	17 *a*	—	Sprue.
52	7·106	17 *c*	—	,,
30	8·425	20	—	,,

Agglutination.

It has been pointed out by Fahraeus (4) that in bloods showing an increased rate of sedimentation there is a greater or less degree of agglutination of the red cells, the more rapidly sedimenting cases showing an agglutination of the cells to a marked extent, and with the production of relatively coarse masses of cells.

This agglutination of the red cells he believes to be due to some agglutinative property resident in the plasma, not of the nature of a specific agglutinin as we know in bacteriological work, but due to some change in the proportions of the proteins of the plasma.

He has pointed out that the agglutinating agent cannot be an agglutinin related to the specific serological ones which are thermo-labile, and this we have been able to confirm. If the plasma is separated from the corpuscles, heated for half an hour at 56° C., and again added to the cells the rate of sedimentation is unaltered.

That agglutination is an important factor in producing an increased rate of sedimentation was well shown in several of our cases, large clumps of agglutinated red cells being observed as sedimentation proceeded. When not seen by this means a test was made for auto-agglutination by the technique of Dyke (5). Particular care was taken in obtaining the patient's serum to maintain the blood at body temperature until the serum was separated.

All the most rapidly sedimenting bloods showed auto-agglutination, and this condition has appeared to us to be undoubtedly the most important factor in causing rapid sedimentation of the red cells in our series of cases.

The Plasma Proteins.

Various authors have from time to time asserted that marked changes in the proportions of the plasma proteins are intimately associated with the phenomenon of accelerated sedimentation. It has been confidently stated that this phenomenon is frequently associated with definite increase in the fibrinogen in the blood, but, as recorded in the previous paper, in none of the fourteen cases then investigated was any definite increase in the percentage of fibrinogen to be detected.

We have since continued this investigation on the fibrinogen content, and

again no increase beyond normal in this protein was found in any of the bloods showing rapid sedimentation, except in one of our cases (No. 23).

Fahraeus, in his classical investigation of the phenomenon of rapid sedimentation, has surveyed the literature on the subject of the protein proportions of the blood in rapidly sedimenting cases, and states that such survey reveals the fact that the fibrinogen or the serum globulin, or both, are increased in those conditions where we know, or may suspect, that the sinking velocity of the red corpuscles is increased.

Chart of Blood Proteins and Formol-gel Tests.

Case.	Diagnosis.	Globulin.	Globulin % of Albumin + Globulin.	Albumin.	Albumin : Globulin Ratio.	Formol-gel.	Fibrinogen.	Sedimentation Ratio.
16 *a*	Kala Azar	5·25	61·8	3·4	0·65	+ +	0·39	210
16 *d*	„ „	3·23	51	3·11	0·96	+ ±	0·263	190
16 *c*	„ „	3·08	49·3	3·18	1·03	+ +	0·23 ?	230
16 *b*	„ „	3·02	45·7	3·6	1·18	+ +	0·317	130
25	Malaria and sepsis	2·29	40	3·45	1·52	neg. (*b*)	0·328	248
19	Postencephalitis	2·14	36·7	3·69	1·72	neg. (? *b*)	0·311	32
21	Trypanosomiasis	1·93	36	3·45	1·78	neg. (*b*)	0·345	120
17 *b*	Sprue	1·68	31	3·63	2·16	neg.	0·328	45
18	Malaria	1·84	30	4·3	2·34	neg.	0·341	15
20	Sprue	1·20	28·8	2·97	2·47	neg.	0·290	30
23	Acute lobar pneumonia	1·44	26·7	3·88	2·69	neg. (*b*)	*0·47*	240
22	? Sprue	1·30	23·2	4·31	3·32	neg.	0·312	51
17 *c*	Sprue	1·27	22·6	4·35	3·42	neg.	0·336	52
	Kala Azar (Wu) (6)	4·92	63·2	2·88	0·58			
Normals	Authors'	1·46	25·4	4·3	2·95	neg.	0·298	8
	Wu (6)	2·09	30·1	4·86	2·32			
	Rohrer (8)		22–46		1·7–3·5			
	Adler (9)		20–45		1·2–4·0			
	Farr and Swanson (10)	2·2		4·9	2·2			

Formol-gel + + indicates a positive reaction. Neg. (*b*) indicates that the test was negative as being diagnostic of Kala Azar, but that a pseudo-positive—i. e. delayed and less milky than the true positive—was seen, as described by Napier (7).

We have further carried out investigations with regard to the proportions of serum albumen and serum globulin in certain of our cases. We have adopted the method of Wu (6) for the determination of the proportions of the various proteins. Criticism has been made of Wu's method, that it does not give strictly accurate figures, but it appeared to us that it was the most convenient method to employ, and further it seemed sufficiently accurate to give, at any rate, a definite indication of the proportions of one protein to another.

It will be seen from this that any definite increase in the proportion of serum globulin is only to be noted in the cases of Kala Azar, the figures in the cases of sprue being definitely low. This increase was only to be expected in view of the fact that cases of Kala Azar give the well-known formol-gel reaction, which is regarded as dependent on an excess of serum globulin in the plasma. This

formol-gel reaction was carried out on the cases of sprue, but with negative results.

Conclusions.

1. The results of laevulose tolerance tests do not suggest that any marked derangement of the liver necessarily accompanies rapid sedimentation.

2. The specific gravity of packed red cells and that of plasma have not been found to show alterations sufficient to account for a great increase in sedimentation-rate.

3. The relative viscosity of the plasma likewise shows no diminution in bloods showing rapid sedimentation. On the other hand, an increased viscosity of the plasma has been observed in Kala Azar, a disease associated with rapid sedimentation.

4. The size of the individual red cell, although found to vary within considerable limits, would not appear to be of any great consequence as a factor influencing the sedimentation-rate.

5. Auto-agglutination seems to have a dominant influence in promoting rapid sedimentation.

6. The ratio of plasma proteins (albumin to globulin) to each other has been found to be appreciably disturbed in cases of Kala Azar—here a globulin increase is associated with a positive formol-gel test, very rapid sedimentation, and auto-agglutination.

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ON CREATINURIA AS A SEQUEL TO FRACTURES OF BONES, AND THE INFLUENCE OF THYROID FEEDING UPON IT AND UPON THE CREATINURIA OF POST-ENCEPHALITIC RIGIDITY [1]

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Historical.

There are reasons for believing that the metabolism of creatine is influenced, directly or indirectly, by the thyroid gland. The occurrence of creatinuria in the state of hyperthyroidism observed in Graves' disease (1) or produced experimentally by the administration of thyroid (2), the increase of the creatine-creatinine ratio of the urine of sheep after the removal of the thyroid and parathyroid glands (3), and possibly the appearance of creatinuria during menstruation and in pregnancy, when the thyroid gland is believed to be more active (4, 5), are some of these.

But the nature of this association between the thyroid and creatine is not understood, nor is it likely to be until more is known regarding the metabolism of creatine itself. Some observations suggest that the creatinuria of hyperthyroidism is related to the diet, more especially the protein components. It has been shown that the output of creatine in subjects manifesting hyperthyroidism is increased when the protein intake is high and is decreased when it is low (6). The output of creatine is also highest in cases of Graves' disease which have an insatiable appetite (7). It would appear from such observations that the creatine has an exogenous origin, and it has been suggested that the influence of the high protein intake is related to the precursors of creatine contained in it (8). Histidine may be one of these, since it has been shown that in rats fed upon hydrolysed casein, freed from arginine and histidine, the output of creatine and creatinine at first increases and then declines; it increases again, however, when histidine is added to the diet, but the addition of arginine has no such effect (9).

Creatinuria, however, occurs when carbohydrate is excluded from the diet (10), and when the body has lost the power of utilizing glucose (11). Since the thyroid exerts an influence upon carbohydrate metabolism, possibly on the power of storing glycogen, the relation of the thyroid to creatinuria may be indirect and due to its influence on the metabolism of carbohydrate.

But there is also the possibility that the action of the thyroid may be exerted upon the creatine contained in the muscles, for much less creatine than normal is

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found in the muscles of fatal cases of Graves' disease (12). Since creatine occurs in combination with phosphoric acid in the phosphagen of muscles (13), it may be that the formation of this substance is influenced in some way by the thyroid autacoid.

During a study of the nitrogenous metabolism in cases of Parkinsonian rigidity following upon epidemic encephalitis, the presence of creatine in the urine was observed (14). We have also found creatine in considerable amounts in the urine of patients in certain cases of fractures. So far as we are aware this has not been recorded previously. Some investigations have been carried out to observe the effect of thyroid upon these types of creatinuria, and the results are recorded in this paper.

The Occurrence of Creatinuria following Fractures of Bones.

This was discovered accidentally. A case of fractured femur was selected as a control for the study of the influence of thyroid feeding on the nitrogen excretion in Parkinsonian rigidity, and it was found that creatine was present in the urine in considerable amount. Other cases were then examined, and the results are given in Table I. The patients were on the ordinary hospital diet and the creatine and creatinine were determined by Folin's method. The figures are the amounts excreted in twenty-four hours; the third column gives the ratio of the nitrogen as creatine to the nitrogen as creatine and creatinine together. The first two cases were compound fractures of the femur; Cases 3 and 4, simple fractures of the femur; in Case 5 the seat of fracture was the pelvis, but the functions of the bladder and rectum were not interfered with. In Case 7 the tibia and fibula were fractured and small amounts of creatine were found for eight days; in Case 6, in which the tibia was fractured, the urine was found to be free from creatine, though examined daily for three weeks. Other cases of fracture of tibia or fibula, or both, were examined without creatine being detected, and some in which small amounts were present. But all the cases of fractured femur examined (Cases 1–4) gave positive results. It is noticeable that the amount of creatinine excreted is apt to be more irregular than it is usual to find it in normal subjects. In some instances, though not in all, this may be due to the difficulty of collecting the whole of the urine excreted. Cases 1–4 were treated by extension, Case 5 was immobilized by bandages. What part atrophy, due to immobilization or extension, plays in the production of the phenomenon, it is not possible to say, but in Case 6, from which no creatine was ever obtained, the treatment was by extension of the limb, and in Case 7, from which creatine was obtained, no extension was employed.

The Influence of Thyroid Feeding on the Creatinuria following Fracture of the Femur.

In order to study this, Case 4 of the above series was placed upon a constant diet of adequate caloric value, free from creatine, creatinine, and nucleo-protein

and containing 15 grm. of nitrogen. The twenty-four hours' output of urine was collected in four periods ending at 7 a.m., 12 noon, 5 p.m., and 9 p.m. The total nitrogen was determined by Kjeldahl's method, uric acid by the Folin-Shaffer method, the creatine and creatinine by the method of Folin. Determinations in duplicate were made for each period. At the end of one week the subject was given thyroideum siccum 16 gr. daily, at 11 a.m. 4 gr., and at 2 and 6 p.m. 6 gr. Eight days later the amount given daily was increased to 24 gr., and this was continued for three days. At this time the patient, who until then had been an ideal subject, co-operating in a most desirable way, refused to continue the diet or take the tablets, so that further detailed observations were no longer possible. For another fortnight, however, the urine was collected each twenty-four hours, and determinations made as before, but the diet was no longer constant or restricted. The patient then went home. Before and during the period of thyroid administration basal metabolism estimations were made by the indirect method with the Douglas bag and the Haldane gas analysis apparatus. The results are given in Table II.

During the six days before thyroid was given the output of nitrogen and uric acid is relatively constant and that of creatinine remarkably so. The creatine varies considerably, though the amount is quite large, the average daily output being 275 mg. As the figures for the different periods of the day show, the rate of excretion is always lowest at night and highest during the morning hours. This is more strikingly shown by the averages for these six days; during the 7 a.m.–12 noon period the average rate of excretion per hour is 15·4 mg., as compared with 8·6 mg. per hour during the night, an increase of 76 per cent. over the nocturnal rate. The average hourly rate falls slightly throughout the day. The ratio of the nitrogen as creatine to the nitrogen as creatine and creatinine together is fairly constant; the average is 14·4 per cent.

During the first two days after the administration of thyroid was begun no change in the creatine output was observed; on the third day it rose to 494 mg., and reached a value of 804 mg. on the eighth day. It fell slightly on subsequent days, but on the first day when the ordinary diet was resumed it rose to 1·04 grm. Thereafter the output gradually diminished to 125 mg. twelve days later, when the patient went home. Eleven days later a sample of urine obtained from the subject as an out-patient contained no creatine. As the creatinine was relatively constant the ration of the creatine rose, and on July 3, when 1·04 grm. of creatine were excreted, the nitrogen as creatine formed 41 per cent. of the nitrogen as creatine and creatinine together.

This effect of the thyroid upon the excretion of creatine is therefore quite remarkable, and it is of interest to note that the increase in the creatine during the first few days was not accompanied by any change in the output in the other nitrogenous constituents examined. Later on, when as a result of the thyroid ingestion the total nitrogen was increased and the basal metabolic rate raised, a small increase in the output of the uric acid was observed. Another interesting change occurs in connexion with the rates of excretion of creatine during the

different periods of the twenty-four hours. This is shown best when the average figures for the periods are examined. The rate is increased for each period, but not uniformly. It is still lowest during the night, but, in contrast to the period before thyroid was given, the rate increases with successive periods throughout the day, so that the highest rate of excretion occurs from 5 to 9 p.m. instead of during the morning hours as before.

Certain other points call for comment. Throughout the whole period of observation, except during the last two days when it fell somewhat, the output of creatinine was remarkably constant; nor was any change in the diurnal tide of excretion comparable to that of the creatine observed.

The rate of excretion of uric acid presents certain features of interest. During the period before thyroid was given the normal diurnal tide does not appear. The morning rate is higher than that observed for the other periods of the day, but not greater than the nocturnal one. The effect of thyroid on the twenty-four hours' output is not marked; a small increase does occur, the average figures before and after thyroid being 0·537 and 0·562 grm. respectively. No marked change in the tide is observed.

The total nitrogen is increased from 18·47 grm., the average daily average before thyroid, to 20·36 grm. on the eighth day of thyroid; the greatest increase in the hourly rate appearing from 5 p.m. to 9 p.m. and from 9 p.m. to 7 a.m. It is also to be observed that the nitrogen balance is negative.

The occurrence of creatinuria in fracture cases is of considerable interest. The subjects are otherwise healthy, and it seems reasonable to associate the disturbance in the metabolism of creatine, which results in its appearance in the urine, with the condition of the limb. It is immobilized with consequent loss of tone, the muscles are damaged by the trauma, and there may be haemorrhage. In addition there is the factor of disuse and atrophy. It is not possible to say what is the particular disturbance which leads to the creatinuria. If the degree of creatinuria is related to the mass of muscle which is functionally inactive, it is interesting to calculate how much creatine would be excreted were all the muscles of the body similarly incapacitated; in Case 4, assuming the muscles of one lower limb to form one-eighth of the body musculature, the creatine output would amount to about 2 grm. per day, and with thyroid this would be increased threefold.

The existence of a tide in the rate of creatine excretion and the absence of one in the case of the uric acid is also of interest. If the creatine tide is related to the normal variations in physiological activity associated with sleep, it is difficult to explain the absence of a uric acid tide. Leathes (15) believes that the uric acid tide is related to the increased tone of the muscles during the daytime, and he has observed a tide in normal individuals remaining in bed, so that the fact that our subject was in bed does not explain the absence of a tide. It is evident that the rate of excretion of uric acid in the case here reported is abnormally high at night, so that the usual diurnal variation is masked. This makes the creatine tide with low rate of excretion at night all the more remark-

able if both creatine and uric acid are related principally to the metabolism of muscle.

There is the possibility that the source of creatine is the food, which in these cases, though it contained no creatine or creatinine, may have contained precursors of creatine. If the figures obtained during the thyroid administration are examined, it will be seen that the rate of excretion of creatine follows that of the total nitrogen, and also that the largest output of creatine that we observed appeared on the first day that the normal diet was resumed, and at a time when the subject was still under the influence of thyroid as shown by the basal metabolic rate on that day. In this connexion it is to be recalled that the degree of creatinuria in hyperthyroidism may be influenced by the amount of protein contained in the diet of subjects manifesting this condition. If the creatine comes from the protein of the diet, it is possible that a relative excess of creatine in the body arises as a result of the large amount of inactive muscle, and that this excess is increased by the action of the thyroid, for Denis (12) found that whereas normal human psoas muscle contained 0·360 per cent. to 0·421 per cent. of creatine, in a case of Graves' disease the concentration of creatine in this muscle was reduced to 0·190 per cent. That loss of function in muscle tissue may be concerned is suggested by the observations of Cameron and Gibson (16) and of Burger (17) on the creatinuria which they found to occur after amputations of limbs.

The Effect of Thyroid Administration upon Creatine Excretion in Parkinsonian Rigidity.

This was studied upon two subjects whose nitrogenous metabolism had been followed out previously in detail over prolonged periods, and who were known to excrete creatine in the urine (14). Here too, the subjects were in bed and on a constant diet containing no creatine, creatinine, or nucleo-protein.

The first of these, Case 8, a male, aged 32 years, wt. 51 kg., was in a state of marked rigidity. After a preliminary period of observation he was given thyroideum siccum in three doses of 4 gr., at 11 a.m., 3 p.m., and 6 p.m. daily. On the tenth day the amount given daily was increased to 16 gr., and this was continued for three days. Observations were continued for the subsequent six days. The results are recorded in Table III.

The amount excreted by this subject normally is less than the output in the cases of fractured femurs, the average for the first six days amounting to 79 mg. One year previously this subject excreted as much as 115 mg. daily. The effect of thyroid produces no increase comparable to that in the fracture case. The average figures show a very slight increase, but actually the amount eliminated on any day during the period of thyroid administration never exceeded the largest amount excreted in twenty-four hours during the preliminary period of observation.

The second subject, Case 9, a male, aged 51 years, wt. 53 kg., was only moderately rigid. After seven days' observation he was given thyroxin in the

following doses: on the first day 1/320 gr., on the second and third days two similar doses, on the next six days three such doses, and on the subsequent two days the amount was increased threefold, i. e. 9/320 gr. daily. Since no effect on the basal metabolism or total nitrogen was observed suspicions fell upon the potency of the thyroxin, so thyroideum siccum was substituted for it. Owing to the large amount of thyroxin which had been taken, the doses of thyroid were small at first and only gradually increased. The doses were as follows: first day, 2 gr.; second and third days, 4 gr.; fourth day, 6 gr.; fifth day, 8 gr.; the next four days, 10 gr.; and the last two, 16 gr. The subject, who had been under observation for over one month, then began to complain of his restricted diet and also of headache, which he attributed to the tablets, so no more thyroid was given. He remained on the diet, however, for another week. The results are set out in Table IV.

As in the other rigid case, the output of creatine during the periods of thyroid and thyroxin administration is practically unchanged; if anything thyroid decreases it slightly. The potency of the thyroxin is questionable, since it had no influence on the basal metabolic rate or the output of nitrogen. The body did respond to the dry thyroid, as shown by the increase in the total nitrogen from an average daily output before thyroid of 12·29 grm. to 14·46 grm. on the last day of thyroid administration, and an increase of 24 per cent. in the basal energy requirements.

The effect of thyroid upon the creatinuria of the fracture case, therefore, contrasts strikingly with the almost negative response in the rigid subjects. It is true that in the latter the daily dose of thyroid was not so large, but the changes in the metabolic rate were of a similar order, about 30 per cent. and 24 per cent., respectively, above the normal level, as compared with 30 per cent. in the former. It seems, therefore, that the metabolic disturbances which give rise to the creatinuria in the two types of cases described are, if not themselves different, at least differently affected by the extract of the thyroid gland.

The Effect of Thyroid Administration on the Excretion of other Nitrogenous Substances.

In these investigations the rate of excretion of total nitrogen and of uric acid in the same four periods of the day and night, as well as for the whole twenty-four hours, was also determined. Any changes in the diurnal fluctuations of the excretion of total nitrogen or uric acid could therefore be observed.

Krause and Cramer (2) have previously shown that the increase in the total nitrogen excretion following the administration of thyroid is largely composed of urea and ammonia, the creatinine and uric acid being only slightly increased, if at all. Our results confirm their observations. The daily output of nitrogen was increased by the course of thyroid, about 16 per cent. in the two rigid cases, about 9 per cent. in the fracture case; the actual additional amounts excreted by the three men were more nearly the same, about 2 grm., because the fracture

case was on a heavier diet. Before the thyroid was given the rate of nitrogen excretion was, as usual, lowest at night; while the thyroid was being taken this difference between night and day rates tended to diminish, because, though the rate of excretion was increased at all periods of the day, it was increased more at night than during the day if an average of the three day periods be taken.

Krause and Cramer (2) also observed a diuresis following thyroid administration in a normal subject. This occurred in our three cases: it was marked in the fracture case, the increase in rate of water excretion appearing in each period of the twenty-four hours (Table II); in the rigid Case 8 (Table III) the diuretic effect appears on May 11–13; in Case 9 (Table IV) it is less marked, though the average figures show a slight increase for the period April 1–6. It is of interest to recall in this connexion the diuretic action of ingested creatine: the most sustained diuretic effect in the three cases occurred in the one who excreted large amounts of creatine in response to thyroid.

Summary.

1. Creatinuria occurs after fracture of bones. The amount of creatine found to be excreted in twenty-four hours in different cases has varied from traces to over 500 mg. It disappears gradually from the urine as healing takes place and the patient is up and about. The hourly rate of excretion is lowest at night. This creatinuria has been observed in four cases of fractured femurs (all that were studied), in some fractures of the tibia and fibula, in a case of fracture of the pelvis, and in a less degree in several, though not all, cases of fracture of the tibia alone.

2. Administration of thyroid gland increased the output of creatine threefold in a case of fracture of the femur. The hourly rate of excretion was increased during each of the four periods into which the twenty-four were divided; this increase was most marked at night, when without thyroid the output was smallest; at other times of the day it was such that the maximum output was shifted from the morning to the evening so as to coincide with the maximum nitrogen output. The increase in the output of creatine preceded any change in the basal metabolism or in the other nitrogenous constituents of the urine. Creatinine was not increased and the uric acid showed only a slight rise.

3. The creatinuria of Parkinsonian rigidity was practically uninfluenced by the administration of thyroid in amounts which caused a similar increase in total nitrogen excretion and basal metabolism to that brought about in the case of fractured femur. The rate of elimination of nitrogen was increased by thyroid during each of the four periods, the effect being relatively especially marked during the night, when the excretion of nitrogen is generally at its lowest.

4. A diuresis was observed in each case as a result of taking thyroid; it was most marked and sustained in the case of fracture of the femur, in which the creatinuria was also increased by taking the drug.

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TABLE I.

	Number of Days after Fracture.	Creatine. Grm. in 24 hrs.	Creatinine. Grm. in 24 hrs.	Ratio %.
Case 1, male, aged 40 years. Fractured femur	13th	0·183	1·145	12·6
	14th	0·195	0·550	24·0
	15th	0·157	0·861	14·0
	16th	0·192	1·370	11·5
	17th	0·108	0·720	11·9
	18th	0·185	0·800	17·3
	Average	*0·170*	*0·909*	*15·2*
Case 2, male, aged 20 years. Fractured femur	12th	0·411	0·980	22·8
	13th	0·555	1·498	25·0
	14th	0·185	1·984	7·7
	15th	0·310	1·118	19·3
	16th	0·278	0·903	21·7
	17th	0·296	0·856	23·7
	18th	0·578	1·271	30·0
	19th	0·289	1·055	20·2
	20th	0·508	1·404	24·6
	Average	*0·403*	*1·135*	*23·4*
Case 3, male, aged 16 years. Fractured femur. Creatine and creatinine free diet " " " "	52nd	0·204	0·578	25·1
	53rd	0·232	0·532	28·3
	54th	0·442	0·508	44·0
	55th	0·355	0·705	31·4
	57th	0·302	0·827	24·8
	58th	0·270	0·648	27·3
	59th	0·243	0·766	22·4
	Average	*0·291*	*0·652*	*29·0*
Case 4, male, aged 45 years. Fractured femur. Creatine and creatinine free diet during whole period	19th	0·214	1·46	11·7
	20th	0·358	1·48	17·8
	21st	0·296	1·45	15·5
	22nd	0·320	1·46	16·6
	23rd	0·300	1·43	15·9
	24th	0·171	1·43	10·8
	Average	*0·275*	*1·45*	*14·4*
Case 5, male, aged 43 years. Fracture of pelvis	29th	0·169	1·40	9·85
	30th	0·128	1·00	10·30
	31st	0·153	—	—
	32nd	0·171	1·28	10·80
	33rd	0·153	1·34	9·35
	34th	0·130	1·30	8·35
	35th	0·087	1·18	6·25
	36th	0·143	1·19	8·30
	Average	*0·142*	*1·24*	*9·03*
Case 6, male, aged 41 years. Fracture of tibia	3rd	No creatine	1·04	—
	4th	"	—	—
	5th	"	1·09	—
	6th	"	1·88	—
	7th	"	1·55	—
	8th	"	1·42	—
	9th	"	1·25	—
	10th	"	1·18	—
	18th	"	—	—
	19th	"	—	—
	Average	"	*1·34*	—
Case 7, male, aged 64 years. Fracture of tibia and fibula	2nd	0·032	0·61	4·40
	3rd	0·051	1·03	4·32
	4th	0·096	0·79	9·94
	5th	0·054	0·81	5·67
	6th	0·027	—	—
	9th	0·046	0·578	6·65
	10th	0·086	0·794	9·01
	Average	*0·056*	*0·769*	*6·66*

Ratio = nitrogen as creatine as % of nitrogen as creatine and creatinine together.

TABLE II. *Fracture of Femur. Thyroid on Creatinuria.*

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 hours.					Basal Metabolism. Calories per sq. metre of Body Surface per hour.	
June.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I	C II.	V.	N.	U.	C I.	C II.	V.		
16	737	26·3	59	13·6	42	818	15·6	66	11·7	35	817	15·3	62	10·3	39	625	21·3	58	4·6	34	*17·30*	*0·484*	*1·46*	*0·214*	*876*	35·9	
17	850	16·4	67	20·0	44	856	18·4	65	16·0	80	974	23·4	64	17·1	75	707	23·0	57	11·1	40	*19·50*	*0·502*	*1·48*	*0·358*	*1042*		
18	765	23·7	58	16·6	65	874	22·0	67	15·4	47	795	20·0	60	9·3	40	700	23·7	59	8·9	39	*18·38*	*0·546*	*1·45*	*0·296*	*1107*		
19	877	26·4	67	19·8	52	722	12·7	52	8·4	46	1133	27·6	79	17·0	70	681	20·3	55	11·0	51	*19·34*	*0·518*	*1·46*	*0·320*	*1285*		
20	685	26·6	58	11·8	61	782	19·1	60	17·0	42	764	21·1	62	14·0	46	728	26·2	59	10·1	42	*17·66*	*0·575*	*1·43*	*0·300*	*1124*		
21	774	25·3	60	9·0	58	688	24·0	58	8·3	36	819	19·7	62	7·	39	806	27·0	60	5·8	43	*18·64*	*0·595*	*1·43*	*0·171*	*1063*	34·6	
Average. June 16–21	*781*	*24·1*	*61*	*15·1*	*54*	*790*	*18·6*	*61*	*12·8*	*47*	*884*	*21·2*	*65*	*12·5*	*51*	*708*	*23·6*	*58*	*8·6*	*41*	*18·46*	*0·537*	*1·45*	*0·276*	*1083*	*35·2*	No thyroid
22	832	26·9	62	11·1	77	692	21·1	57	7·9	42	823	26·3	60	15·0	47	782	26·0	60	6·6	53	*18·74*	*0·605*	*1·44*	*0·221*	*1238*	—	Thyroid, gr.
23	767	28·3	60	13·0	64	667	15·0	54	15·0	37	790	17·5	63	10·0	45	745	27·5	55	9·3	53	*17·78*	*0·561*	*1·37*	*0·274*	*1222*	—	xvi daily
24	796	27·8	58	21·0	65	817	22·7	59	24·6	56	943	17·7	64	25·0	61	691	22·4	59	16·6	55	*18·76*	*0·547*	*1·43*	*0·494*	*1396*	—	,,
25	786	29·1	60	27·0	87	780	17·9	60	28·1	63	915	18·0	63	32·0	65	719	23·7	61	22·0	58	*18·68*	*0·544*	*1·46*	*0·626*	*1506*	36·6	,,
26	797	31·8	60	32·0	62	806	21·3	63	34·0	48	1027	15·0	70	34·6	57	713	22·3	54	20·1	43	*19·25*	*0·548*	*1·43*	*0·669*	*1206*	34·8	,,
27	799	27·2	59	31·7	54	779	24·5	60	34·5	47	878	17·8	60	28·6	52	880	24·1	59	14·4	60	*20·20*	*0·570*	*1·42*	*0·589*	*1303*	34·8	,,
Average. June 24–7	*794*	*29·0*	*59*	*27·9*	*67*	*795*	*21·6*	*60*	*30·3*	*53*	*941*	*17·1*	*64*	*30·0*	*59*	*751*	*23·1*	*58*	*18·3*	*54*	*19·22*	*0·552*	*1·43*	*0·594*	*1352*	*35·4*	Thyroid
28	860	25·8	58	38·2	68	792	18·3	59	24·0	56	976	22·4	57	38·0	64	794	26·0	57	29·0	54	*20·11*	*0·570*	*1·39*	*0·751*	*1413*	35·0	,,
29	866	30·2	60	39·8	74	858	20·9	58	36·0	69	945	27·5	60	39·0	77	788	27·0	57	26·8	69	*20·29*	*0·635*	*1·41*	*0·804*	*1717*	38·2	,,
30	750	26·5	56	24·0	74	849	21·1	61	32·0	58	1291	30·9	82	44·4	101	720	22·0	51	23·0	58	*20·36*	*0·586*	*1·42*	*0·688*	*1643*	40·0	Thyroid, gr.
July																											xxiv daily
1	877	23·7	52	30·7	72	756	30·4	61	37·0	84	742	18·7	48	27·6	69	672	21·7	51	27·8	60	*18·85*	*0·562*	*1·27*	*0·728*	*1657*	41·2	,,
2	485	13·0	35	25·0	37	785	21·4	55	24·0	60	887	22·9	56	38·0	69	666	18·9	51	29·5	48	*16·76*	*0·452*	*1·19*	*0·705*	*1238*	44·8	,,
3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	*18·94*	*0·630*	*1·34*	*1·04*	*1510*	46·6	No thyroid. Ordinary diet
Average. June 28 to July 2	*768*	*23·8*	*52*	*31·5*	*65*	*808*	*22·4*	*59*	*30·6*	*65*	*968*	*24·4*	*61*	*37·4*	*76*	*728*	*23·2*	*53*	*27·2*	*58*	*19·27*	*0·561*	*1·34*	*0·735*	*1534*	*39·8*	Thyroid

Creatine output on succeeding days—July 4, 0·459 July 7, 0·424 July 10, 0·244 July 13, 0·172 July 27, no creatine
,, 5, 0·554 ,, 8, 0·207 ,, 11, 0·207 ,, 14, 0·117
,, 6, 0·278 ,, 9, 0·126 ,, 12, 0·057 ,, 15, 0·125

N = nitrogen. U = uric acid. C I = creatinine. C II = creatine. V = volume. Rates expressed in mg. per hour. Total output in grammes.

TABLE III. *Parkinsonian Rigidity. Thyroid on Creatinuria.*

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 hours.					Basal Metabolism. Calories per sq. metre of Body Surface per hour.	
April.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	
25	510	20·6	58	2·4	77	580	19·0	59	3·5	62	656	17·0	55	3·8	45	517	10·8	51	1·5	43	*13·24*	*0·376*	*1·31*	*0·059*	*1306*	42·2	
26	554	20·1	55	3·6	111	575	17·4	54	3·4	62	769	17·0	56	4·6	61	524	11·7	48	4·7	30	*13·96*	*0·373*	*1·24*	*0·101*	*1407*	41·7	
27	494	19·6	55	1·2	71	531	15·5	52	4·0	80	575	18·1	54	1·9	41	446	12·8	48	1·8	26	*11·89*	*0·376*	*1·23*	*0·055*	*1184*	40·5	
28	436	25·1	54	4·1	45	584	19·2	55	4·0	97	769	20·6	64	6·5	59	542	14·3	55	4·2	45	*13·49*	*0·434*	*1·34*	*0·108*	*1406*	42·8	
29	447	19·5	53	3·0	62	485	17·2	54	2·4	36	669	21·0	59	2·5	47	430	11·3	48	4·2	29	*11·60*	*0·380*	*1·25*	*0·079*	*967*	41·5	
30	474	14·0	53	3·9	82	483	19·0	56	2·7	66	609	15·0	53	4·2	47	411	8·4	49	2·1	28	*11·33*	*0·309*	*1·25*	*0·072*	*1207*	41·7	
Average. April 25–30	*486*	19·8	*55*	*3·0*	*75*	*539*	*17·9*	*55*	*3·4*	*67*	*674*	*18·1*	*57*	*3·9*	*50*	*478*	*11·5*	*50*	*3·0*	*35*	*12·58*	*0·375*	*1·27*	*0·079*	*1246*	*41·7*	No thyroid
May 1	445	19·6	52	2·5	81	527	18·4	59	5·0	50	663	17·4	52	5·0	48	456	12·8	48	3·3	47	*12·80*	*0·387*	*1·25*	*0·090*	*1318*	47	Thyroid, gr.
2	578	21·1	60	3·5	100	553	16·0	56	1·5	62	572	14·1	53	3·2	42	433	10·1	48	2·6	32	*12·28*	*0·342*	*1·28*	*0·064*	*1303*	47·5	xii daily
3	430	21·7	56	1·9	42	538	15·2	54	3·3	50	697	16·3	58	3·6	45	504	14·3	51	3·5	28	*12·67*	*0·393*	*1·29*	*0·076*	*930*	45·9	,,
4	476	21·1	55	2·4	33	576	20·0	59	5·0	30	714	20·7	59	2·9	31	501	14·6	51	3·5	25	*13·13*	*0·434*	*1·31*	*0·082*	*715*	—	,,
5	489	22·0	57	3·3	28	590	20·1	56	3·6	29	816	19·6	61	3·4	39	429	10·2	36	3·2	20	*12·72*	*0·391*	*1·16*	*0·079*	*635*	50·6	,,
6	542	20·2	58	3·4	35	629	20·2	61	3·4	44	667	16·0	53	2·3	51	524	12·5	52	4·2	36	*13·76*	*0·391*	*1·32*	*0·085*	*962*	51·1	,,
7	476	17·0	56	2·4	40	588	16·3	63	1·5	51	466	11·4	38	2·1	28	597	16·4	59	3·7	36	*13·15*	*0·377*	*1·33*	*0·065*	*938*	49·3	,,
Average. May 1–7	*491*	*20·4*	*56*	*2·8*	*51*	*571*	*17·9*	*58*	*3·3*	*45*	*656*	*16·6*	*53*	*3·2*	*41*	*492*	*12·9*	*49*	*3·4*	*32*	*12·93*	*0·388*	*1·28*	*0·077*	*971*	*48·5*	Thyroid
9	557	23·0	61	2·6	40	600	14·8	47	1·4	30	764	23·2	59	4·4	40	585	12·4	47	5·2	35	*14·54*	*0·407*	*1·25*	*0·089*	*863*	51·1	,,
10	561	23·5	62	3·1	52	607	16·5	49	4·8	33	835	13·8	56	2·5	57	542	11·7	48	2·8	34	*14·57*	*0·377*	*1·28*	*0·076*	*991*	53·3	,,
11	579	18·6	54	4·3	48	652	13·3	53	2·8	84	707	13·8	53	3·7	66	553	12·0	50	3·4	45	*14·51*	*0·335*	*1·25*	*0·083*	*1375*	55·2	18 gr.
12	484	16·5	53	3·7	66	668	14·4	51	3·4	69	775	9·5	53	4·3	56	609	11·9	49	5·2	56	*14·95*	*0·310*	*1·25*	*0·092*	*1459*	—	,,
13	656	12·1	57	4·6	153	601	14·5	53	2·5	46	764	12·1	54	2·9	50	588	13·4	49	4·2	48	*14·97*	*0·315*	*1·26*	*0·089*	*1672*	50·3	,,
14	299	11·0	31	1·8	31	930	23·0	79	5·9	72	722	17·7	53	5·1	52	548	10·4	47	3·4	34	*14·51*	*0·343*	*1·23*	*0·092*	*1061*	—	Thyroid discontinued
Average. May 9–14	*523*	*17·4*	*54*	*3·3*	*65*	*676*	*16·1*	*55*	*3·5*	*56*	*761*	*15·0*	*55*	*3·8*	*53*	*571*	*12·0*	*48*	*4·0*	*42*	*14·67*	*0·348*	*1·25*	*0·087*	*1237*	*52·5*	Thyroid
15	362	22·7	36	—	49	600	15·0	47	2·4	35	838	17·4	56	3·5	55	613	10·4	52	3·3	37	*14·19*	*0·364*	*1·16*	*0·059*	*1012*	50·8	
16	550	18·9	58	—	58	609	11·5	58	2·2	36	682	12·3	53	2·7	43	527	11·3	48	4·3	36	*13·79*	*0·314*	*1·27*	*0·064*	*1005*	—	
17	465	19·4	55	2·1	28	465	19·4	55	2·1	28	850	23·1	67	9·1	43	511	12·8	50	2·7	24	*13·16*	*0·414*	*1·32*	*0·084*	*690*	—	
18 and 19	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	*12·10*	*0·369*	*1·29*	*0·076*	—	—	
20	644	14	52	3·8	80	—	—	—	—	—	566	17·8	55	2·0	38	428	10·4	49	3·4	28	*12·59*	*0·334*	*1·25*	*0·070*	*1028*	—	

N = nitrogen. U = uric acid. C I = creatinine. C II = creatine. V = volume. Rates expressed in mg. per hour. Total output in grammes.

TABLE IV. *Parkinsonian Rigidity. Thyroid on Creatinuria.*

Date.	7 a.m.–12 noon.					12 noon–5 p.m.					5–9 p.m.					9 p.m.–7 a.m.					Total in 24 hours.					Basal Metabolism. Calories per sq. metre of Body Surface per hour.	
Mar.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.	N.	U.	C I.	C II.	V.		
1	463	17·1	36	2·5	41	628	16	44	2·3	51	587	9·4	37	3·7	44	461	9	37	1·3	31·6	*12·42*	*0·292*	*0·919*	*0·052*	*951*	—	
2	424	12·1	32·3	3·0	60	608	13·5	47·5	4·0	54	582	9·7	37·5	0·0	64	450	10·2	36·4	2·6	38	*11·99*	*0·269*	*0·912*	*0·060*	*1205*	33·5	
3	552	18·4	40	5·5	83	545	9·3	40	4·0	41	636	10·7	37	5·1	62·5	455	8·1	36·5	1·5	42	*12·58*	*0·262*	*0·903*	*0·082*	*1290*	34·8	
4	543	14·9	42	5·1	95	573	19·1	41	2·4	60	690	9·1	41	4·1	82	506	10·7	37·3	1·2	44	*13·40*	*0·313*	*0·947*	*0·078*	*1544*	34·6	
5	504	14·7	41	4·8	89	545	15·2	36·3	3·1	61·5	608	11·6	39	1·5	64	414	7·8	36·0	3·7	35	*11·82*	*0·274*	*0·900*	*0·082*	*1360*	—	
6	424	16	41	2·6	30	594	18·5	43·8	3·2	52	571	7·4	40	2·3	37	376	9·4	34	2·4	22	*11·14*	*0·296*	*0·927*	*0·062*	*773*	33·5	
7	426	16	35	3·3	33	674	16·6	47	3·7	47	580	13·2	37	3·1	39	487	9·2	35	2·9	33	*12·68*	*0·308*	*0·913*	*0·077*	*887*	33·8	
Averages.																											
Mar. 1–7	*477*	*15·6*	*38*	*3·8*	*62*	*595*	*15·5*	*43*	*3·2*	*52*	*608*	*10·1*	*38*	*2·8*	*56*	*450*	*9·2*	*36*	*2·2*	*35*	*12·29*	*0·288*	*0·917*	*0·070*	*1144*	—	No thyroxin
„ 8–18	*482*	*14·3*	*36*	*3·2*	*60*	*610*	*16·2*	*44*	*3·0*	*60*	*587*	*11·3*	*38*	*2·4*	*57*	*452*	*9·3*	*37*	*2·9*	*35*	*12·27*	*0·269*	*0·922*	*0·064*	*1176*	—	Thyroxin
„ 19–21	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	*11·75*	*0·236*	*0·927*	*0·059*	*904*	—	No thyroxin
„ 22–25	*445*	*14·7*	*36*	*1·9*	*58*	*647*	*13·9*	*42*	*5·2*	*58*	*577*	*13·1*	*37*	*1·3*	*54*	*432*	*9·5*	*37*	*3·2*	*38*	*12·09*	*0·290*	*0·908*	*0·063*	*1181*	—	Thyroxin
27	306	10·3	27·3	2·2	27	736	23	56	2·3	47	635	9·6	38	—	54	476	7·6	37	2·0	43	*12·51*	*0·281*	*0·931*	*0·042*	*1016*	33·8	Thyroid, gr. ii
28	532	15·0	37	3·5	74	600	12·1	45	1·1	45	594	9·0	3·8	3·8	47·5	481	8·2	36	3·5	42	*12·84*	*0·253*	*0·883*	*0·073*	*1205*	33·4	Thyroid, gr. iv
29	415	15·4	34	2·2	60	641	16·4	48	3·6	59	516	11·0	39	3·7	43	286	6·9	24	2·4	28	*10·21*	*0·272*	*0·805*	*0·067*	*1043*	34·1	Thyroid, gr. iv
30	668	21·8	29	1·0	64	700	15·7	49	2·5	54	595	9·4	39	3·1	90·5	484	9·5	39	1·6	40	*14·06*	*0·320*	*0·932*	*0·046*	*1347*	34·6	Thyroid, gr. vi
31	460	17·2	42	1·6	57	564	6·3	43	2·1	33	600	6·1	40·5	2·1	46	449	11·4	37	—	34	*12·01*	*0·256*	*0·962*	*0·027*	*978*	36·6	Thyroid, gr. viii
Average.																											
27–31	*476*	*17·9*	*34*	*2·1*	*56*	*648*	*14·7*	*48*	*2·3*	*47*	*588*	*9·0*	*39*	*2·5*	*56*	*434*	*8·7*	*35*	*1·9*	*37*	*12·32*	*0·276*	*0·904*	*0·051*	*1118*	—	Thyroid

TABLE IV (*continued*).

Apr. 1	468	17·7	39	3·0	45	606	11·1	40·4	—	40·4	682	11·8	37	1·1	67	533	10·7	38	1·9	55	*13·43*	*0·298*	*0·922*	*0·038*	*1242*	34·7	Thyroid, gr. x
2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	*12·35*	*0·220*	*0·865*	*0·042*	*1281*	35·7	Thyroid, gr. x
3	434	11·4	40	2·0	40	557	7·8	42	2	42	631	6·2	37	2·7	63	491	10·3	36·8	2·3	49	*12·39*	*0·224*	*0·926*	*0·054*	*1149*	36·3	Thyroid, gr. x
4	527	15·5	40	2·6	59	690	11·7	43	3·2	67	656	11·5	38	2·3	66	491	10·9	39	2·3	44	*13·63*	*0·290*	*0·958*	*0·062*	*1331*	34·6	Thyroid, gr. x
5	528	21·6	43·4	2·1	52	645	17·2	43	3·0	60	745	13·7	42	2·7	71	497	11·5	38	4·1	43	*13·81*	*0·363*	*0·980*	*0·076*	*1269*	33·9	Thyroid, gr. xvi
6	548	17·0	44	3·2	53	711	11·1	43	2·8	48	756	9·9	38	—	80	524	10·5	39	4·0	43	*14·56*	*0·285*	*0·969*	*0·070*	*1249*	38·4	Thyroid, gr. xvi
Average. Apr. 1–6	*501*	*16·6*	*41*	*2·6*	*50*	*642*	*11·7*	*42*	*2·2*	*51*	*694*	*10·6*	*38*	*1·8*	*69*	*517*	*10·8*	*38*	*2·9*	*47*	*13·36*	*0·280*	*0·937*	*0·057*	*1253*	—	Thyroid
7	510	11·0	43	1·5	42	630	8·8	44	3·4	37	577	8·7	35	3·7	38	495	11·8	35	4·0	31	*12·96*	*0·254*	*0·920*	*0·079*	*858*	41·5	No thyroid
8	568	21·2	42	2·7	36	557	14·7	36	4·2	31	679	16·6	41	1·8	41	499	12·4	34	2·6	31	*13·33*	*0·370*	*0·894*	*0·068*	*806*	36·6	„ „
9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	*11·72*	*0·220*	*0·871*	*0·064*	*778*	—	
10	487	19·0	40	2·7	34	569	6·0	43	1·7	31	602	11·2	38	2·0	36	417	8·6	34	2·5	25	*11·85*	*0·255*	*0·912*	*0·045*	*720*	39·8	„ „
11	450	15·0	41	2·3	33	558	4·0	40	2·7	27	613	8·5	39	3·3	39	449	10·4	36	2·4	30	*11·98*	*0·232*	*0·914*	*0·062*	*759*	34·4	„ „
12	460	15·7	38	4·0	42	604	17·5	41	5·0	43	678	15·1	38	3·0	59	411	9·3	35	3·6	28	*12·14*	*0·319*	*0·899*	*0·092*	*937*	32·9	„ „
13	499	17·8	42	3·0	44	574	13·3	42	3·6	40	667	13·0	43	2·4	84	399	8·7	35	4·7	29	*12·03*	*0·293*	*0·940*	*0·089*	*1044*	35·8	„ „
Average. 9–13	*474*	*16·9*	*40*	*3·0*	*38*	*576*	*10·2*	*41*	*3·2*	*35*	*640*	*11·9*	*39*	*2·7*	*54*	*419*	*9·2*	*35*	*3·3*	*28*	*11·94*	*0·264*	*0·907*	*0·070*	*848*	—	

N = nitrogen. U = uric acid. C I = creatinine. C II = creatine. V = volume. Rates expressed in mg. per hour. Total output in grammes.

ACUTE EOSINOPHILIC LEUKAEMIA AND EOSINOPHILIC ERYTHRO-LEUKAEMIA[1]

By JOHN HAY and WILLIAM HOWEL EVANS
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With Plates 6 and 7

In recent years there have been reports of a small number of cases which appear to be related to chronic myelogenous leukaemia, with this difference, that the leucocytes in the peripheral blood and in the internal organs were of adult type, and not immature forms. The cases would appear to be extremely rare, and the only example in British literature is found in the valuable report and discussion by McDonald and Shaw. In the great majority the predominant cell has been the polynuclear eosinophil; this was so in six clear cases, and in two doubtful ones. In addition one case with predominance of the polynuclear neutrophil has been described. Clinically, all the cases were of the chronic type. We have recently observed two cases apparently belonging to this group. The first was a case clinically identical with acute myelogenous leukaemia, and showing splenomegaly, general glandular enlargement, a high leucocytosis, and intense infiltration of all the internal organs with eosinophil cells. The second case, which ran a more chronic course, showed the combination of polycythaemia with an increased white count composed largely of polynuclear eosinophils. It is well known that many cases of polycythaemia vera show a varying degree of leucocytosis, always of the granular series, frequently with immature cells such as myelocytes and occasionally myeloblasts. In the celebrated case of Blumenthal the polycythaemia was combined with myeloid leukaemia, the blood showing 36 per cent. of myelocytes and the marrow at necropsy leucoblastic activity apparently in excess of erythroblastic.

A necropsy was obtained in our two cases. From the study of the clinical condition, the blood, and the morbid histology, it appears that the first case is an unusual form of leukaemia originating in the eosinophil system, and is in every way comparable to acute myelogenous leukaemia. The second case is regarded as one of polycythaemia with eosinophilia which can be compared with 'eosinophilic leukaemia' in the same way that Blumenthal's syndrome may be compared with the ordinary forms of myelogenous leukaemia.

[1] Received August 15, 1928.

Cases.

Case I. Acute eosinophilic leukaemia.

The patient, A. E., a clergyman, aged 41, gave a bad family history of tuberculosis, and as a young man had suffered from tuberculous pleurisy. In recent years, though never robust, he had been in comparatively good health, and just before his fatal illness had been away on holiday, and feeling 'very fit'. About the middle of October 1925 he complained of sore throat, and enlargement of the tonsils and submental and cervical lymph nodes was found. The throat at first suggested diphtheria, but the enlargement of the tonsils progressed rapidly with superficial ulceration, and enlargement of the inguinal lymph nodes and the spleen was noticed a few days after the onset. From the first the patient was profoundly prostrated, and the pulse was rapid, though there was practically no fever until the terminal stages.

He was admitted to the Royal Infirmary, Liverpool, on October 23, 1925, under the care of Dr. John Owen. A blood smear taken on admission showed a well-marked leucocytosis with gross eosinophilia, and a complete examination of the blood was made on October 28, i. e. the day before death. While in hospital the pulse-rate was about 140, and there was occasional evening rise of temperature to about 100° F., but not above. Just before death a shower of petechiae occurred about the trunk and legs. He died on October 29, 1925, rather less than three weeks from the date of the first complaint.

Blood findings: blood culture sterile.

28.10.25	Haemoglobin	60 per cent.
	Reds	3,975,000
	Reticulated reds	0·72 per cent.
	Whites	72,187
	Platelets	69,000
	Bleeding time	8 min. +

Wassermann reaction negative.

Van den Bergh negative, direct and indirect.

Urine: trace albumin. Deposit—a few red cells, no casts. No excess of urobilin.

Stools: two examinations negative for parasites, protozoa, and ova.

Differential white count:

Polymorphs	4·2 per cent.	} 4·6 per cent.	
Neut. myelocytes	0·4 per cent.		
Lymphocytes	6·0 „ „		
Mononuclears	1·4 „ „		
Basophils			
Polymorphs	3·5 „ „	} 4·3 per cent.	
Myelocytes	0·8 „ „		
Eosinophils			
Polymorphs	75·5 „ „	} 83·7 per cent.	
Myelocytes	3·8 „ „		
Metamyelocytes	4·4 „ „		

Two megaloblasts and three normoblasts seen in counting 1,000 white cells.

A differential count of 1,000 eosinophils, counted as regards the nucleus, showed:

Myelocytes	5·0 per cent.
Metamyelocytes	5·1 „ „
1 lobe	4·2 „ „
2 lobes	66·9 „ „
3 lobes	18·2 „ „
4 lobes	0·6 „ „

Note: the term 'myelocytes' includes all those cells with round or oval nuclei; the term 'metamyelocytes', those cells with nuclei showing simple indentation without division into lobes.

The eosinophil cells varied considerably in size, both polynuclear and myelocyte forms. On the whole they seemed to be rather larger than normal. There was great variation in the number and size of the granules. Some cells were completely filled with large granules, others contained fine granules and in a small proportion the cell was largely devoid of granules, showing large clear areas of cytoplasm. This latter character was particularly well marked in the cells classed as myelocytes (see Pl. 7, Fig. 7). A few cells were seen containing eosinophil granules and a smaller number of basophil granulations.

Necropsy, 30.10.25.

Permission for post-mortem examination was at first unconditionally refused, but owing to the exertions of Dr. D. R. Evans and Dr. T. E. Jones of Liverpool, permission was finally obtained to make an incision for the purpose of removing the spleen. All the organs were removed from this incision. As permission to excise a piece of bone was refused, it was only possible to remove a small fragment of rib, from which a few smears of the marrow were made.

The body showed well-marked emaciation, with numerous small petechial haemorrhages distributed over the trunk and extremities. Similar haemorrhages were found beneath the visceral pericardium and the mucous membrane of the pelvis of both kidneys.

Lungs: there were healed tuberculous scars at both apices, with old fibrous and partially calcified pleurisy over the right lower and middle lobes, in front adherent to the parietal pericardium. No evidence of active tuberculosis.

Heart: 11 oz., macroscopically normal. All valves normal: coronary arteries and aorta normal.

Liver: 60 oz., somewhat congested, firm and of a deep yellow colour.

Kidneys: 5½ oz. each; pyramids congested: cortex presented a curious marbled red and white appearance.

Spleen: 20 oz., was rather soft, and on section it was chocolate brown in colour, the Malpighian bodies not being visible.

Lymph glands: the *cervical and inguinal* groups were generally enlarged, the individual glands averaging the size of a pigeon's egg. They were firm and white in colour, a number in each situation showing small fresh punctiform haemorrhages.

Retroperitoneal: the iliac and aortic glands formed a continuous chain, the average size about that of an almond. Some of the glands contained small recent haemorrhages.

The mesenteric glands were not enlarged. The Peyer's patches and solitary follicles were normal in size, and the bronchial glands were not enlarged in any striking way.

The tonsils were considerably enlarged, and were covered with large superficial sloughing ulcers.

The intestinal contents did not show any macroscopic parasites, and subsequent microscopical examination was negative for parasites, ova, and protozoa.

Morbid histology: pieces were selected from the spleen, the lymph glands in various sites, liver, kidneys, and lungs. They were fixed in 4 per cent. buffered formalin, cut in paraffin, and stained by haematoxylin and eosin, van Gieson,

eosin and methylene blue, Goodpasture's stain for oxdyase granules and for free iron. The bone-marrow smears were stained by Leishman's stain and by the panoptic method.

Bone-marrow (Pl. 7, Fig. 8): the fragment obtained from a rib was greyish-white in colour, and was almost entirely cellular. The smears showed a marked excess of leucoblastic tissue, in which eosinophils were very prominent, myelocyte and polynuclear forms being roughly equal. Neutrophil and basophil myelocytes and polynuclears could be detected in small numbers. There were also numerous non-granular cells, apparently myeloblasts. Occasional megaloblasts and normoblasts could be seen. Fat was practically absent. A few Charcot-Leyden crystals were visible.

Spleen (Pl. 6, Figs. 3 and 4): smears from the freshly-cut surface of the organ showed enormous numbers of Charcot-Leyden crystals. The lymphoid follicles were almost completely obscured and infiltrated by eosinophil cells, with which the pulp also was crowded. The sinuses contained large numbers of eosinophils. In all these situations the predominant cells were polynuclear eosinophils, and only a very small proportion could be regarded as myelocytes. Charcot-Leyden crystals were also prominent in the sections. Phagocytosis of eosinophil cells by mononuclear cells of the pulp and the endothelial cells lining the sinuses could be seen, showing various stages in the destruction of the cells. Oxyphil granules were scattered throughout. A very occasional nucleated red cell could be seen in the sinuses. There was no evidence of erythropoiesis. There was no evidence of siderosis. There was not any reticular over-growth, or evidence of fibrosis.

We consider that the appearances do not afford any evidence of active formation of eosinophils in the spleen, and are due to an infiltration from the blood-stream.

Lymph glands (Pl. 6, Figs. 5 and 6), from all situations: the appearances were practically identical with those of the spleen. The lymphoid follicles were completely obscured by the cellular infiltration. In several of the glands sections showed large extravasations of blood into the pulp. As in the spleen, the vast majority of the eosinophil cells were polynuclear, and myelocytes were scanty. There was not any reticular over-growth or fibrosis. In one or two sections occasional Charcot-Leyden crystals were seen.

Liver (Pl. 6. Figs. 1 and 2): periportal infiltration with the same type of cells. The liver cells were separated by distended capillaries, many of which contained eosinophils.

Kidney: diffuse infiltration with eosinophils.

Lungs: numerous perivascular areas of infiltration with eosinophils, notably, around the bronchial vessels.

Sections of deltoid, diaphragm, and rectus femoris were negative for trichinosis.

None of the organs showed, macroscopically or microscopically, any evidence of active tuberculosis or of any other lesions which would account for the eosinophilia.

In our view this case is an example of acute myelogenous leukaemia, the peculiarity of which lies in the fact that the infiltration of the peripheral blood and internal organs is with adult eosinophils. As far as is possible, other known causes of eosinophilia were excluded, and, as already stated, there was not any histological evidence in the internal organs of a local production of eosinophils. It

would therefore appear that the eosinophilic infiltration arose from the activity of the bone-marrow. It is curious that in this, as in other reported cases, the eosinophils were mainly of adult type, with few primitive forms. For this reason, considering the acute nature of the disease (three weeks) this case seems unique in medical literature. In the following summary of the reported cases the author's descriptive title and conclusions are appended.

Stillman (1912). '*Myeloid leukaemia with preponderance of eosinophil cells.*'

A male, aged 27, in the New York Hospital in 1911, showed anaemia, moderate enlargement of the liver and spleen, and of the cervical, inguinal, and epitrochlear glands. Serum, Wassermann strongly positive: the urine contained a trace of albumin and a few casts. No parasites or ova found in the stools.

The white cells varied from 118,000 to 165,000 per c.mm. The eosinophils varied from 85·8 to 91 per cent. A differential count when the leucocyte count was 165,000 gave the following result:

Polymorphs	3·8 per cent.		
Lymphocytes	4·2 „ „		
Transitionals	0·8 „ „		
'Mesoblasts'	0·2 „ „		
Eosinophils:			
Polymorphs	69·8 „ „	}	91·4
Metamyelocytes	19·4 „ „		
Myelocytes	1·8 „ „		

The eosinophils were rather larger than normal, and the granules rather smaller. Normoblasts were present in the proportion of 2 per 100 leucocytes. It was not stated that trichinae were excluded. The patient was lost sight of and no more is known about him.

McDonald and Shaw comment, 'assuming that the " metamyelocytes " in the account were only varieties of the eosinophils, and that the true myelocytes were only 1·8 per cent., as stated, the case can hardly be described as an ordinary leukaemia and would apparently find a place in the special group we are now considering'.

Beifield and Barnes (1916). '*Severe anaemia with eosinophilia.*'

A German, aged 68, entered the County Hospital in Chicago 27.11.15 and died 23.1.16. No necropsy. Vagabond with gross pediculosis. Skin of trunk and extremities eczematous. Very anaemic: facies of lemon-yellow colour. Well-marked emphysema and asthenia. Serum and cerebrospinal fluid, Wassermann negative. Urine: trace of albumin and a few granular and hyaline casts.

The blood counts, several of which are recorded, showed a red count averaging about 1,600,000. Haemoglobin (Sahli) 46 to 42 per cent., giving a colour index from 1·4 to 1·3. Macrocytosis and poikilocytosis present, also an occasional megaloblast. Platelets practically absent in early counts, very scanty in the later ones.

Whites varied from 4,200 to 5,500, the eosinophils from 28 to 53 per cent. in four counts (one count showed only 9 per cent.). Eosinophils noted as incompletely filled with granules. During the period of observation the polymorphs dropped from 34 to 16 per cent. and the lymphocytes rose from 13 to 55 per cent. Myelocytes were noted, 1 per cent. in 2 counts, myeloblasts 1–2 per cent.

The gastric test meal showed achlorhydria: stomach X-ray normal. Stools repeatedly negative for parasites, trichiniasis not excluded.

The authors consider that either the emphysema or the skin condition might explain the eosinophilia but not the pernicious type of anaemia.

No conclusion can of course be drawn from this case in the absence of the histology of the haemopoietic organs. The small white count does not suggest leukaemia, and there is not any note of enlargement of spleen, lymphatic glands, or liver.

Giffin (1919). 'Persistent eosinophilia with hyperleucocytosis and splenomegaly.'

Male, aged 31. First seen at the Mayo Clinic in March 1913, the illness having begun at least a year previously with dyspnoea and pain in the left chest. When first seen the patient exhibited cardiac failure and anasarca. The spleen, liver, and axillary glands were enlarged. The white count was 15,400 with 66 per cent. of eosinophils, myelocytes 'very rare'. Examination of the stools negative for parasites; piece of excised muscle negative for trichina. An axillary gland excised at this time showed numerous eosinophil polymorphs and eosinophil myelocytes. Splenectomy June 1914. Spleen weighed 2,110 grm. Histologically the Malpighian corpuscles were intact: the pulp was crowded with eosinophil polymorphs and a lesser number of eosinophil myelocytes.

After splenectomy the white count rose rapidly, reaching 208,000 in ten months. The eosinophils varied from 79 to 90 per cent.: myelocytes about 0·2 to 0·3 per cent. after the count reached 100,000. In October 1917, i.e. three years after the splenectomy, the whites were 135,000 with 87 per cent. eosinophils. The patient died with general anasarca in January 1919, the last count, in November 1918, being 81,000 with 84 per cent. eosinophils.

Necropsy showed broncho-pneumonia, chronic pleurisy, obliterative pericarditis, fibrous perihepatitis, cirrhosis of the liver, and general lymphoid hyperplasia. Giffin notes that 'the obliterative pericarditis and fibrous perihepatitis were probably of long standing, and much of the symptomatology during the last six years of the patient's life could be attributed to the cardiac and hepatic disease'. Microscopically the bone-marrow was hyperplastic and showed great numbers of eosinophil polynuclears which outnumbered eosinophil myelocytes in the proportion of 10 to 3. Erythropoiesis was very deficient. Lymph gland from region of head of pancreas showed a very well-marked infiltration with eosinophil polynuclears and a few eosinophil and neutrophil myelocytes. This gland showed a much grosser infiltration with eosinophils than did the spleen removed 4½ years earlier.

Giffin, discussing his case together with that of Stillman, is opposed to the idea of leukaemia, chiefly on account of the predominance of mature cells in all sites, the presence of gross cardiac and liver disease, the absence of hyperleucocytosis before splenectomy, and the long duration (seven years). He finally concludes, 'I am inclined to regard the case as an instance of eosinophilic hyperleucocytosis, the blood picture of which was remarkably altered by splenectomy'.

Shapiro (1919). 'Eosinophilic (polymorphonuclear) leukaemia.'

Male, aged 49 at death. Under observation between March 1916 and April 1917. Illness presumably began five years previously. When first seen the patient was emaciated, spleen three fingers' breadth below the left costal margin, the liver enlarged, and the inguinal and epitrochlear lymph nodes palpable. There was not any obvious disease of the heart or lungs. Serum, Wassermann strongly positive; stools negative for parasites; sputum negative for tubercle

bacilli. Urine—a little albumin, trace of sugar, and a few hyaline casts. Death occurred, with extreme dyspnoea, oedema of the legs and face, and ascites, in April 1917. The blood count when first examined showed 19,800 whites with 70 per cent. of polynuclear eosinophils. It gradually increased until just before death it reached 236,000, with 79 per cent. of polynuclear eosinophils and five per cent. of eosinophil myelocytes, 1 per cent. of basophil myelocytes. In addition, the author noticed 6 per cent. of cells resembling polynuclear eosinophils, but without granules. The eosinophils present are described as (*a*) normal adult cells with two- or three-lobed nuclei, (*b*) adult cells incompletely filled with granules, and (*c*) myelocytes, also incompletely filled with granules.

Necropsy showed ascites and enlarged liver and spleen. The heart was not enlarged, but the right ventricle was about half filled with a large organized ante-mortem clot. The cut section of the bone-marrow was solid and greyish red. Microscopically the bone-marrow was very cellular, and showed large numbers of eosinophils, both myelocyte and polynuclear forms, also numerous myeloblasts. The eosinophil cells in the bone-marrow were frequently incompletely filled with granules. The spleen showed diminution of the Malpighian bodies and the pulp was loosely filled with cells, chiefly eosinophil leucocytes. The liver, lungs, and heart were infiltrated with eosinophils. It is not stated that trichinosis was excluded.

The author's conclusion is, 'I believe this is a case of leukaemia arising in the eosinophil system of cells'.

Tuohy (1920). '*Splenomegaly with polymorphonuclear neutrophil hyperleucocytosis*'.

Female, aged 58, previous history uneventful. Pain in left side in May 1917, splenomegaly detected shortly after. Had worn a pessary for uterine prolapse for some years, with local irritation. This, however, subsided under treatment, without affecting the blood picture. The spleen extended beyond the umbilicus; there was no glandular enlargement. The white cells numbered 65,000 with 99 per cent. of polymorphs, red cells 4,200,000, haemoglobin 80 per cent.

Splenectomy was performed in December 1917 for increasing anaemia and discomfort. The white cells rose sharply after splenectomy (240,000 in three days), but twenty-six days after the operation the count was 45,000 with the same polynuclear picture. The patient was apparently well until some five months later, when she died of acute pneumonia. Unfortunately there is not any report on the excised spleen no necropsy.

The author comments, 'This case even more than Giffin's would seem to indicate that under certain conditions there can be a calling forth of particular types of leucocytes, normal in form and structure without any apparent tendency to ultimate failure on the part of bone marrow (as shown by a mobilization of embryonal or immature forms) seeming to exemplify the ability of bone marrow to hyperfunction in a benign way'.

Aubertin and Giroux (1921). '*Existe-t-il une leucémie à eosinophiles?*'

A male, age not stated, first seen in 1910. He died in 1914. Clinical evidence of congenital pulmonary stenosis with dyspnoea and cyanosis. Right ventricle hypertrophied. Spleen just palpable. Liver palpable only when the heart failed. He had repeated attacks of cardiac failure, with enlarged liver, ascites, and cyanosis. Necropsy confirmed the pulmonary stenosis, the blood-forming organs were not examined. The stools repeatedly negative for parasites: serological tests for hydatids negative: Wassermann negative: had had malaria.

Blood: Reds averaged 4,500,000 never 'polyglobulie'. Whites varied

between 6,900 and 26,000 most frequently about 10,000. Differential count—one only given:

Polymorphs	19·75	per cent.
Eosinophils—		
Polynuclear	65·75	„
Myelocytes	0·75	„
Mononuclears	11·25	„
Lymphocytes	3·0	„
Large mononuclears	1·25	„

The authors, discussing their case together with those of Stillman and Giffin, regard theirs and Giffin's as cases of eosinophilia associated with the anoxaemia of the cardiac lesions, though they admit there may be a leukaemia of adult cells.

McDonald and Shaw (1922). '*Persistent eosinophilia with splenomegaly.*'

Male, aged 46, first seen at the Royal Victoria Hospital, Newcastle-on-Tyne in July 1921. For some years vague digestive troubles and latterly loss of weight. The enlarged spleen was discovered in course of routine examination. The white count then showed 34,000 whites with 71 per cent. of eosinophils. The abdomen was explored for possible hydatid cysts, and the spleen being found to be quite mobile was removed (July 1921). The excised spleen weighed 1,276 grm. The Malpighian bodies were largely fibrosed and were extensively infiltrated with eosinophil cells. The pulp was highly cellular and also crowded with eosinophils. In all situations the eosinophil polynuclears largely exceeded eosinophil myelocytes. A similar appearance was seen in two small haemolymph glands found in the hilum of the spleen. The authors saw no evidence of active formation of eosinophil cells in the spleen or haemolymph glands, and regarded the infiltration seen in these organs as a filtration from the blood. After splenectomy the white count steadily increased. The last observation recorded, in September 1922, i. e. fourteen months later, showing 138,000 cells with 84 per cent. eosinophils. The large majority of the eosinophil cells showed the typical adult two or three lobed nuclei. A small number of eosinophil myelocytes was also present, varying from 2·7 per cent. to 8·7 per cent. of the total eosinophils, and 0·7 to 4·7 of the total white count. In the later counts an occasional neutrophil and basophil myelocyte was seen. The eosinophils varied considerably in size and their granules also varied in size and depth of staining. Some cells showed large clear areas of cytoplasm devoid of granules, others were vacuolated. Basophilic granulations were sometimes observed mixed with the eosinophilic ones. A small proportion of normoblasts and megaloblasts was constantly present: the platelets appeared to be normal. During the period of observation repeated tests of the stools were negative for parasites. The Wassermann was negative and the blood showed no evidence of protozoal infection. Trichinosis was not excluded. When last seen, in September 1922, there was some enlargement of the cervical axillary lymph glands. The liver was not enlarged. We have since heard that the patient is dead: no further details have been published.

The authors conclude, 'we are inclined to the view that we have here a condition of the bone-marrow primarily affecting the eosinophilic elements—a condition therefore more allied to a true leukaemia, but of a most unusual type'.

Alexander (1924). '*Splenomegaly with hyperleucocytosis.*'

Male, aged 52 at his death in 1921. First seen in 1919. Onset in 1912 with anaemia, dyspnoea, and splenomegaly. Splenectomy was performed in

1914 for increasing anaemia. The only blood record at this time was whites 9,400, polymorphs 72 per cent., lymphocytes 38 per cent. (*sic*).

Alexander later examined the spleen, which was badly deteriorated from poor fixing. It weighed 2,200 grm. and histologically showed considerable fibrosis and was infiltrated with eosinophil and neutrophil polynuclears, myelocytes being scanty. When seen in 1919, i. e. five years after the splenectomy, the patient showed extreme anaemia with dyspnoea and asthenia. The liver was 8 cm. below the costal margin. The superficial lymph nodes were not palpable. The white cells were 150,000 with 24 per cent. of eosinophils and 60 per cent. polymorphs.

The white count fluctuated, until death twenty months later, between 19,000 and 70,000, most frequently from 30,000 to 50,000. The eosinophils constantly averaged about 30 per cent., the polymorphs 40 to 60 per cent. A small proportion of neutrophil, eosinophil, and basophil myelocytes, averaging together about 2 per cent. of the total whites, was constantly present. The red count varied between 1,200,000 and 4,300,000. Nucleated red cells were usually present in large numbers. Death from broncho-pneumonia in April 1921.

Necropsy. Liver much enlarged, bone-marrow yellowish, heart fatty, lymph glands generally showed no gross enlargement. Histologically, the bone-marrow showed numerous cells of polynuclear type, mostly eosinophil, and numerous myelocytes in process of division. The lymph glands were densely infiltrated with eosinophil and neutrophil leucocytes. The liver showed infiltration of the portal spaces, and the capillaries were stuffed with eosinophil and neutrophil polynuclears. No mention of exclusion of intestinal parasites or trichinae.

The author discusses his case together with those of Giffin, Aubertin and Giroux, McDonald and Shaw, and Tuohy. He considers it to be an atypical form of myelogenous leukaemia.

Bass (1925). '*Unusual eosinophilia with splenomegaly.*'

In a female child aged 6 splenomegaly had been noticed at the age of 2. She had otitis media and tonsillectomy at the age of 5: pansinusitis shortly before the observations, which were made between February and April 1924.

Clinically she exhibited old rickets. Spleen two fingers' breadth below the left costal margin, liver three fingers' breadth below the right costal margin. Cervical lymph glands slightly enlarged. Serum, Wassermann negative; no parasites in the stools. In the next three months the cervical glands enlarged, and the inguinal and axillary glands became palpable. Death occurred in June 1924 from broncho-pneumonia; no necropsy. A count on 6.4.24 showed:

Haemoglobin	80 per cent.
Reds	4,830,000.
Platelets	310,000.
Whites	25,600.
Differential—	
Polymorphs	18·3 per cent.
Lymphocytes	9·6 ,,
Mononuclears	1·3 ,,
Eosinophil—	
Polynuclears	64·0 ,,
Myelocytes	6·3 ,,
Basophils	0·5 ,,

Of these nine cases, No. 2 (Beifeld and Barnes) and 6 (Aubertin and Giroux) appear to be separate from the group now under consideration. The case of Beifeld and Barnes seems in the first place, from the blood picture and

achlorhydria to be undoubtedly a case of pernicious anaemia. The white cells in the peripheral blood show a low count, and there is not any mention of enlargement of the spleen or lymph glands. As possible factors for the eosinophilia, anoxaemia (emphysema) and parasitic skin lesions may be invoked. It is therefore unnecessary to discuss this case farther than to note that it is the only example of a combination of pernicious anaemia and high eosinophilia we have found.

In the case of Aubertin and Giroux (which has been discussed by Giffin, McDonald and Shaw, and Alexander) the authors considered that the anoxaemia of the congenital heart lesion was the most probable cause of the condition. The white count at no stage reached massive proportions, the spleen is described as 'just palpable', and there was not any enlargement of the lymph glands. Nor is there any note that the condition progressed in any way during the four years the patient was under observation, as would be expected in the average case of myelogenous leukaemia, and as was, in fact, noted in most of the reports now under consideration. As trichiniasis was not excluded, and the histological changes in the blood-forming organs are not available, we entirely agree with McDonald and Shaw that 'it is doubtful if this case can be considered as belonging to the group we are now considering'.

There are therefore seven cases left for discussion, excluding our own, six of which suggest a condition clinically and pathologically allied to myelogenous leukaemia, with a preponderance of a single type of cell of normal adult character.

Five of these were eosinophilic, one (Tuohy) neutrophilic. In the seventh case (Alexander) there is evidence of increase of both eosinophils and neutrophils.

Clinically all these cases were of a chronic character, as set out below: Stillman—duration unknown; Giffin—total 7 years, 4½ after splenectomy; Shapiro—6 years; McDonald and Shaw—uncertain, several years; Alexander—9 years, 7 after splenectomy; Bass—uncertain, but splenomegaly 4 years before; Tuohy—*circa* 1 year.

On the whole the average duration appears to be somewhat longer than that of the average case of myelogenous leukaemia, characterized by the presence of myelocytes and other immature cells, and this is in accordance with what might be expected when the condition is characterized by hyperplasia of adult cells. The case reported here is acute and stands in the same relation to the others as acute myelogenous leukaemia does to chronic myelogenous leukaemia, with this noteworthy difference—that there is not any corresponding immaturity of the cells.

Aetiological and Clinical.

There does not appear to be any common aetiological factor. Clinically, all the cases are characterized by splenomegaly, and in the cases of Stillman, Shapiro, Giffin, MacDonald and Shaw, Bass, and our own, enlargement of various groups of lymphatic glands is mentioned. In the cases of Stillman and Shapiro it is stated that the serum Wassermann was strongly positive, but a very similar

clinical picture was presented in the cases of McDonald and Shaw, and Tuohy without any evidence of syphilis. Giffin's patient suffered from a combination of chronic pleurisy, pericarditis, and perihepatitis, but it is difficult to imagine that these lesions could account for the distinctive splenomegaly, glandular enlargement, and specific marrow hyperplasia. Certainly such syndromes (Pick, Concato) may exist without eosinophilia. There is no statement as to any special factor in the cases of Tuohy and Bass. In three cases (Giffin, Alexander, and McDonald and Shaw) splenectomy was performed, and in each case a notable increase in the white cells *followed* the splenectomy. This led Giffin to suggest that his case was an example of 'hyperleucocytosis in which the blood picture was modified by splenectomy'. Yet a similar progressive increase occurred without splenectomy in the cases of Shapiro and Stillman—it is possible that it may have been precipitated more quickly by the removal of the phagocytic tissue of the spleen, seeing that, both in the accounts of McDonald and Shaw and our own, phagocytosis and destruction of the eosinophils by reticulum and endothelial cells of the spleen is specifically mentioned. Nor does it appear that splenectomy led to any *qualitative* change in the blood.

In the case of Alexander the position is not so clear, as unfortunately precise details of the blood condition before splenectomy are wanting; there is some cogency in the argument that in this case the loss of the spleen may have modified the marrow activity. In the case of Bass nothing save rickets, otitis media, and pansinusitis is mentioned, and though the report lacks evidence of the morbid histology, the progressive glandular enlargement is distinctly suggestive of a leukaemic condition. In our case, as already indicated, no causal factor was forthcoming.

The Blood Picture.

The blood picture in all the cases, with the exception of those of Tuohy and Alexander, is practically identical, yet both these cases are parallel to the others. In the case of Tuohy there was leucocytosis with 99 per cent. of mature polynuclears, and in the case of Alexander, leucocytosis with approximately 90 per cent. of the cells divided between mature polynuclears and eosinophils. The other six cases all show varying degrees of leucocytosis with high eosinophil count. The eosinophils are predominantly of mature type, and small proportions only of immature forms are noted. In the cases of Stillman, Shapiro, McDonald and Shaw, and our own, it is noted that the oxyphil granules varied in size and staining, and that some of the cells were incompletely filled, rather suggesting a functional difficulty on the part of the tissues in the production of adequate supplies of the oxyphil material. In the case of McDonald and Shaw and in our own the presence of basophilic granulations in certain of the eosinophil cells is mentioned.

Morbid Histology.

Descriptions of the morbid anatomy are given by Shapiro (necropsy), Giffin (necropsy), McDonald and Shaw (excised spleen and lymph glands), Alexander

(necropsy), and our own (necropsy). It may be stated categorically that they all show a picture identical with that described in myelogenous leukaemia, with the exception that the cellular infiltrations are all described as being of polynuclear or adult eosinophil cells. Had the descriptions been of myelocytic infiltration no question could have been raised as to the leukaemic nature of the cases. Alexander's case only differs in the admixture of adult neutrophils and eosinophils, and in this way forms a link connecting the eosinophilic cases with Tuohy's neutrophil case. All the descriptions strongly indicate the marrow as the origin of the eosinophils and suggest that the appearances in the various internal organs were due to a filtration from the blood-stream.

From a review of this group of cases we are convinced that there is a category of cases indistinguishable from myelogenous leukaemia except for the presence of selective disturbance of individual mature elements. So far as the few cases yet reported go, only neutrophil and eosinophil examples are at hand, but it should not be surprising to hear of a similar case with predominance of the basophil elements.

We regard our case as of the acute, and all the other cases as of the chronic type of the condition, and it is interesting and surprising to find that, despite its fulminating nature, the eosinophil cells were no more immature than the others.

As McDonald and Shaw remark, it seems idle to attempt to draw a distinction between an eosinophil leucocytosis in response to a definite toxic influence, and a true leukaemic condition. In practically all the reports given there is satisfactory exclusion of the usually recognized causes of eosinophilia. The underlying cause of leukaemia is as yet unsettled; while from all considerations it seems reasonable to describe it as a neoplasm of the haemopoietic tissue, it must be admitted that the ultimate stimulus to neoplastic growth in the case of the marrow is just as obscure as in the case of any other body tissue.

Case I. Eosinophilic erythro-leukaemia.

M. R., a woman aged 54 at the time of her death, was under observation from August 1925 to April 1926. She was married and had two healthy children followed by three miscarriages. In 1911 she suffered from a continued fever of uncertain diagnosis (laboratory tests negative for enteric group). Apart from this her previous history was uneventful.

On admission she complained of about two years' vague symptoms of loss of energy, dull pain under the left ribs, occasional vomiting, and loss of four stone in weight. Apart from this she had had several attacks of acute pain in the left loin, followed by dysuria and frequency without haematuria. She stated that she had noticed a dusky 'bloated' appearance of the face increasing in the last year or two, but was quite certain that this did not exist before the beginning of the illness.

Objectively she showed the typical plethoric facies of polycythaemia, with moderate cyanosis. The nails were slightly curved, but there was no clubbing of the fingers. She showed obvious signs of loss of weight—her present weight was 7 st. 12 lb. The spleen was 3 in. below the left costal margin, firm and not tender, the liver 2 in. below the right costal margin, and rather soft. There was no enlargement of lymphatic glands. The lungs were normal. The heart was not enlarged, the aortic second sound was normal and there were no bruits. The radial arteries could be rolled but showed no marked thickening. The radial

blood-pressure was 145 systolic and 105 diastolic. The fundus showed engorgement and tortuosity of the retinal veins ; no haemorrhages were present.

Four days after admission she had an attack of violent pain in the left loin, lasting for several hours, with vomiting, and temperature of 102° F. Attacks of pain continued intermittently for the next two days, leaving the left side of the abdomen intensely tender to the touch. Six days after the onset of the attack she passed a small uric acid stone, with abatement of all the symptoms. At this time the urine contained a heavy deposit of pus and showed a well-marked colon bacilluria. Following the passage of the stone the pyuria diminished considerably, but the urine constantly showed a trace of albumin and a few granular and hyaline casts.

The stools were repeatedly examined for parasites with negative results. The Wassermann reaction was negative.

The blood findings are shown in Tables I and II and will be described in a separate section.

The clinical condition was characterized by steady loss of strength. The splenomegaly progressed. A note on 15.1.26 states, 'Spleen at umbilicus, firm, liver at umbilicus, rather tender'.

From 12.11.25 to 8.3.26 the patient was treated by X-rays to the spleen, in all seventeen exposures being given. Clinically, no benefit appeared to result, and no significant change in the blood picture, except possibly a slight decline in the total white count.

In March 1926 the patient returned complaining of dyspnoea and swelling of the legs. She was extremely cyanosed and breathless. From this time till her death she exhibited signs of progressive cardiac failure—oedema of the legs, enlargement of the liver and spleen, ascites, and hydrothorax, for which no obvious cause could be found. She died with general anasarca 13.5.26.

It is of interest to note that, from the time when cardiac weakness first manifested itself, the blood-platelets, hitherto normal, progressively diminished (see Table I). At the necropsy the left ventricle was found to be half filled with ante-mortem clot, the probable cause of the cardiac embarrassment. It is difficult to resist the conclusion that the platelets were progressively removed coincident with the growth of the clot, though this was not suspected during life.

The blood. The blood was first examined on August 10, 1925, four days before the passage of the stone. As will be seen from Table I and the Chart, the red cell count was 7,400,000, HB 89 per cent. (Dare). It is interesting to note that the white count of 62,180 was the highest of the series, and that its height was due mainly to the polynuclear neutrophils. Following the acute stage of the urinary infection the polynuclears largely diminished, and from that time onwards the blood findings were remarkably constant.

Red cells. The red cells varied between 8,375,000 (maximum) and 6,920,000 (minimum), the haemoglobin averaged about 100 per cent. There was a constant increase in the reticulated red cells, and normoblasts and a smaller number of megaloblasts were constantly present. Polychromasia was constant, as also varying degrees of poikilocytosis and microcytosis.

Fragility of the red cells. The fragility of the red cells in NaCl solutions was tested several times, and gave similar results on each occasion. Haemolysis began at 0·56–0·5 per cent. NaCl, but was not complete until 0·28 per cent. NaCl. The normal control (W.H.E.) showed the figures 0·42 per cent. NaCl and 0·28 per cent. NaCl respectively, so that the patient's cells show a lengthening of the resistance span but a normal point of maximum resistance. This agrees with the findings of Minot and Buckman (1923).

Van den Bergh test was done on several occasions and always showed a weakly positive indirect reaction. The urine constantly contained a moderate excess of urobilin.

The white cells. During the eight months' observation there was little

essential change in the white cell picture. The count varied between 16,000 (min.) and 46,000 (max.), being for the most part round about 30,000. The lower counts towards the end may possibly have been due to the X-ray treatment (seventeen exposures were given between 12.11.25 and 8.3.26).

The most striking thing in the white cell picture is the well-marked and persistent increase in the eosinophil cells, which, as shown in Table II, were for the most part of adult type. Throughout the period of observation eosinophil myelocytes were scanty. The cells, however, show somewhat simpler nuclear forms than did those of our first case, and in the successive counts this tendency to simplification became somewhat more marked, possibly indicating the turning out of a more primitive type of cell—if the nuclear lobulation is a guide to the age of the cell. The eosinophils varied in size, the majority tending to be rather larger than normal, and there was considerable variation in the size and staining of the granules. At no time, however, was the picture that of typical leukaemia, and it bears a striking resemblance to that shown by the 'eosinophilic leukaemia' group. In addition, it will be noticed that a few neutrophil and basophil myelocytes were invariably present.

The blood picture thus points to a dual disturbance of the marrow—viz. an increased erythroblastic activity, and an increased leucoblastic activity specially shown in respect of the eosinophil cells.

The platelets at first showed counts about the upper level of normal. In March 1926 a sharp drop occurred and from this point there was a progressive diminution. The clotting time in the earlier stages was always normal. The viscosity was measured by Dr. F. Earlam on one occasion and gave a value of 7·2 by Hess's method (normal adult female = 4·40).

Necropsy, 14.5.26. The body showed general anasarca. The peritoneum contained about 20 pints of fluid, the right pleura about 4 pints, the left pleura about 2 pints.

Lungs. The lungs were congested and oedematous.

Heart. The heart weighed 13 oz.; the parietal and visceral pericardium showed numerous petechial haemorrhages. There was a considerable excess of pericardial fluid with early fibrinous pericarditis at the base. The right heart was dilated, and a small ante-mortem thrombus the size of a hazel-nut was found in the right auricular appendage. The left ventricle was nearly half filled with a tough, rather shaggy, wedge-shaped ante-mortem clot adherent to the apex. At the extreme apex some parts of the clot were soft and yellowish, elsewhere it was firmly adherent to the muscle. The valves were normal, and the aorta and coronaries were remarkably healthy.

In passing, it is of some interest to recall the similar cardiac clot found in the right ventricle in Shapiro's case (p. 172), and the similar terminal clinical symptoms of dyspnoea, ascites, and general oedema.

Kidneys, 4 oz. each, macroscopically resembled the small red granular contracted kidney. There were three calculi the size of peas, in the substance of the right kidney, projecting into the pelvis. One rather larger calculus in the pelvis of the left kidney. The pelves of the kidneys and the bladder were considerably injected.

The liver, 76 oz., was deeply congested.

The spleen, 20 oz., was firm and cyanotic. On section the Malphigian bodies were not visible and there were no infarcts. On dissection the splenic artery and vein appeared normal, and there were not any thrombi in any part of the portal circulation.

The lymph glands in all situations were difficult to find and appeared to be reduced in size.

Bone-marrow. One section through the middle of the femur was permitted. It was cellular, mainly reddish, but mottled with white, and fat appeared

practically absent. A similar appearance was noted in the section through the ribs and sternum.

Intestinal contents. Macroscopically showed no evidence of parasites and subsequent microscopical examination was entirely negative.

Morbid histology. Pieces were selected from the spleen, lymph glands in various sites, liver, kidneys, lungs, heart, and bone-marrow. Pieces of muscle from the deltoid, diaphragm, and rectus femoris were also selected. All the tissues were fixed in 4 per cent. buffered formalin. Unfortunately the bottles containing pieces of liver and the lymphatic glands were thrown away. The loss of the liver is particularly regrettable, but probably little was to be learned from the glands, as, owing to their small size in all situations, little important change seemed likely to have occurred in them. We were thus left with sections from the spleen, bone-marrow, kidney, heart, and lungs. The sections were stained by haematoxylin and eosin, van Gieson, eosin and methylene blue, Goodpasture's stain for oxydase granules and for free iron.

The most striking general histological change in all the tissues examined was their extraordinary vascularity and the prominence everywhere of the capillary vessels. In many areas in the spleen the sections might have been the counterpart of the polycythaemic spleen figured on p. 502 of Eppinger's 'Die hepato-Lienalen Erkrankungen'. It is possible that the prolonged period of cardiac failure may to some extent have helped to exaggerate this general congestion, but there can be no doubt that the extraordinary vascularity of the organs in polycythaemia is due to the increase of the total blood volume.

Bone-marrow (Pl. 7, Figs. 11 and 12). The bone-marrow was entirely cellular and practically no fat was present. All the capillaries were prominent and filled with cells. The cellular tissue between the capillaries showed an almost equal division into the erythroblastic and leucoblastic elements. Many megaloblasts and normoblasts were present.

The white cells showed a number of large non-granular cells probably myeloblasts. Eosinophil cells were numerous and consisted of approximately equal numbers of myelocyte and polynuclear forms. Neutrophil myelocytes and polynuclears were also present in considerable numbers, and occasional basophils were noted. Fair numbers of megakaryocytes could be detected.

Spleen (Pl. 7, Figs. 9 and 10). The capsule was greatly thickened and the trabeculae thickened and hyaline. The organ was extremely vascular, and in certain areas there were large extravasations of red cells into the interstices of the pulp. In other parts the pulp showed a considerable degree of fibrosis, and was loosely infiltrated with eosinophil and neutrophil polynuclears. The Malpighian arteries exhibited hyaline thickening, and the great majority of the lymphoid follicles were extensively fibrosed and infiltrated with leucocytes. In all situations the bulk of the cells were eosinophil and neutrophil polynuclears—only a very occasional myelocyte was to be seen. No evidence of local leucopoiesis was apparent.

In the sinuses and in the pulp a number of nucleated red cells, both normoblasts and megaloblasts, were to be seen. This is not surprising when we recall the large numbers of these cells present in the peripheral blood shortly before death (*vide* Table). There was not any evidence of local erythropoiesis. A small amount of haemosiderin was present in the endothelial cells of the sinuses and in the mononuclear cells of the pulp, also small amounts extracellularly in the pulp.

There was also slight evidence of phagocytosis of eosinophils by the endothelial and mononuclear cells.

Smears of the fresh spleen showed a few Charcot-Leyden crystals: none were observed in sections.

The general picture of the spleen may be summed up as vascularity, fibrosis, atrophy of lymphoid structures, and diffuse eosinophilic infiltration.

Heart. Sections through the apex of the left ventricle and adherent clot showed the latter to be organizing and pigmented. Elsewhere the muscle showed the same vascularity noted in the other organs.

Kidneys again showed enormous vascularity and well-marked chronic nephritic changes. In addition, there was a diffuse infiltration of the interstitial tissue, both of the cortex and medulla, with eosinophils.

Muscles. Pieces of deltoid, diaphragm, and rectus femoris were negative for trichina.

This may be regarded as polycythaemia vera, with excessive leucoblastic activity especially of the eosinophil cells, and, following Di Guglielmo, it may be termed 'eosinophilic erythro-leukaemia'.

In the present state of knowledge it seems rational to regard polycythaemia vera and myelogenous leukaemia as neoplastic disorders of the red and white cell elements of the bone-marrow, respectively.

It is well known that there are many links connecting the two diseases, and we consider that these links form the best argument supporting the dualist view of the origin of the blood-cells—that is to say, the conception of separate stem-cells for (*a*) the red cells and the granular white cells, and for (*b*) the non-granular white cells.

The links are:

1. Cases of myelogeneous leukaemia constantly show nucleated and other immature forms of red cells in the peripheral blood, and at autopsy the marrow frequently shows well-marked erythroblastic activity.

2. Cases of polycythaemia vera constantly show a varying degree of leucocytosis, always of the granular series, frequently with the presence of immature cells such as myelocytes and myeloblasts. At autopsy many observers state that, while there is an undoubted general increase of red marrow, there is striking evidence of equal leucoblastic activity.

3. Certain cases show a combination of polycythaemia with leukaemia, as in the celebrated case of Blumenthal.

4. Sometimes cases of long-standing polycythaemia have become anaemic, with leukaemic blood change.

5. In other cases long-standing leukaemia has developed a polycythaemic stage.

As examples of *polycythaemia with leucocytosis* we may quote the following:

Turk (1904) described three cases. The red cells varied from 8,380,000 to 9,965,000 and the white cells from 16,500 to 33,800 with occasional myelocytes.

Rencki (1908) describes three cases in which the red cells varied from

6–10,000,000, and the white counts from 13,000 to 38,000, myelocytes 0·7 per cent.–3·1 per cent. Rencki also mentions a case where, following splenectomy for polycythaemia (reds 7,000,000, whites 10,000), the red cells varied between 5 and 7,000,000 and the whites reached 114,000 with occasional myelocytes. At necropsy the marrow was red, with great activity, both of erythroblastic and leucoblastic elements.

Nicola (1908). Reds 8,000,000, whites increased 'up to 250 per cent.', myelocytes 1·6 per cent.

Cautley (1908). Red cells varied between 9 and 10,000,000, white cells between 59,000 and 91,000. Polymorphs 93 per cent. and myelocytes 0·8 per cent.

Rosin (1908). Patient a woman. Red cells at first 10,000,000. Some years later the red cells fell to 3,500,000, but the whites rose to 52,000 with 80 per cent. polymorphs, 12 per cent. eosinophils, no myelocytes.

Parkes Weber and Bode (1927). Red cells 7,100,000, whites 56,000: no immature forms: no splenomegaly.

Cases illustrating the combined picture of *polycythaemia with myeloid leukaemia* (Di Guglielmo's 'erythro-leukaemia').

In Blumenthal's (1905) classical case, the patient had 11,450,000 red cells and 16,300 white cells with 36 per cent. of neutrophil myelocytes. At necropsy the marrow showed leucoblastic activity in excess of erythroblastic.

Parkes Weber and Watson (1904) described a case in which the red cells were 9–11,000,000 and although the white count was only 7–12,000, at necropsy the marrow showed intense leucoblastic as well as erythroblastic activity.

Parkes Weber (1927) also quotes Meyer and Edens, who reported similar necropsy findings in a case where the red cells were 6,120,000 and the white cells 68,000.

Brieger and Forschbach (1922) quote an intensely interesting case of Wolff of Breslau. In this case a normal spleen was removed for traumatic rupture. In a few months signs of erythraemia appeared, and four years later the red cells numbered 9,200,000, whites 41,000, myelocytes 3 per cent. Thirteen years after the splenectomy the reds were 6,060,000, whites 50,400, and the patient is described as of 'typical polycythaemic appearance, clubbed fingers: typical fundus'.

Parrisius (1923) mentions a case in which, when first seen, the red cells numbered 9,000,000 and the white cells 15,000. Three years later the red cells were 6,000,000, and the whites 91,000 with 4 per cent. of myelocytes and a few myeloblasts.

Pancoast and Pendergrass (1922). The patient had 7,000,000 red cells with 9,400 whites, immediately before the start of X-ray treatment. After radiation the red cells dropped somewhat, but the white cells rose and myelocytes were constantly present. Three years later the reds were 5,000,000, whites 17,000, myelocytes 2 per cent.

Hay and Evans (1926). A case jointly observed by us in 1926, ran the clinical course of acute myeloblastic leukaemia, being fatal in approximately six weeks. In spite of severe generalized purpura the red cells numbered 6,240,000, and the white cells 218,000 with 2·8 per cent. neutrophil myelocytes, and *circa* 80 per cent. of myeloblasts. No necropsy was obtained.

With regard to *polycythaemic cases becoming leukaemic.*

Minot and Buckman (1923) mentioned three cases of long-standing polycythaemia (red cell counts varying between 7–11,000,000), who gradually developed anaemia ($2\frac{1}{2}$–$3\frac{1}{2}$ millions); at the same time the white counts rose, averaging 35,000, with 10 per cent. of myelocytes, and myeloblasts up to 15 per cent. One case came to necropsy and the organs resembled those of myeloid leukaemia.

Brieger and Forschbach (1922) described a case whose earlier counts showed reds 14,000,000 and whites 10,000.

Under X-ray treatment the counts were reduced to 4,500,000 and 5,700 respectively, when the patient suddenly developed acute myeloblastic leukaemia (reds 1,670,000, whites 255,000, enormous numbers of myeloblasts). No necropsy was permitted.

The same authors mention Hirschfeld's case, where a long-standing polycythaemia became transformed into leukaemia with myelaemic blood picture (whites 20,000, myelocytes 12 per cent.).

Parkes Weber and Bode (1927) quote a case of Herxheimer in which splenomegalic polycythaemia vera was present for years before the development of fatal myeloblastic leukaemia.

Hedinius (1914). This case in the earlier stages showed a combination of polycythaemia with leucocytosis and a small percentage of myelocytes. After a prolonged treatment with X-rays and benzol, the patient became anaemic. The white count varied, but myelocytes were constantly present. At necropsy the marrow and spleen showed marked leucoblastic reaction with myelocytes, neutrophils, and eosinophils.

Cases of *leukaemia showing a polycythaemic* stage are rather less common.

Winter (1908) describes a case originally diagnosed as chronic myeloid leukaemia (reds 4,800,000, whites 22,660, myelocytes 30 per cent.). After X-ray treatment the patient, 2½ years later, showed reds 8,292,000, whites 23,000, myelocytes absent. The end of the case is not stated.

In a case observed by one of us (W. H. E.) in 1926 the patient at one time showed reds 2,700,000, whites 460,000. Five months after the start of X-ray treatment the red cells were 6,400,000 and the white cells 20,000.

Di Guglielmo quoted by Parkes Weber and Bode (1927) reported a case of myeloid leukaemia with rise in the red count to 7,200,000 in eight months.

The impression we have gained from the study of these cases is that bone-marrow activity as exhibited in leukaemia and erythraemia is much more variable than is usually supposed.

Critical analysis of our leukaemic case and the other similar reports leaves no doubt that we are dealing with a hyperplastic disturbance of the bone-marrow in respect of the eosinophil polynuclear cells. Tuohy's case, though regrettably incomplete, suggests the possibility of similar hyperactivity in respect of the neutrophil polynuclear. (McDonald and Shaw mention that they have heard of a case which they cannot vouch for, of hyperleucocytosis with predominance of the basophils. If such a case could be established we would then have the evidence of selective activity of the marrow in respect of all three of its known granulocyte products.) In the eosinophilic cases, which are by far the most numerous, most of the reports adequately exclude parasites and other known causes of eosinophilia. In every other detail, that is, in the degree of eosinophilia, its persistence and increasing intensity, the increasing splenomegaly and glandular enlargement, and the morbid anatomy and histology, the cases exactly square with the picture of myelogenous leukaemia. We consider that there is not any justification for the description of a new clinical entity such as 'hyperleucocytosis with splenomegaly', favoured by Giffin, Tuohy, and Alexander, but that the cases are examples of myelogenous leukaemia only differing

from the usually recognized type in the predominance of a single, and mature, cell type. The previously reported cases are examples of the chronic type, and our case fills a gap by supplying an example of an acute type. It is of great interest to note that in our case, despite the acute nature, the predominant cells were no more immature than in the more chronic ones.

Passing to our second case, it has been shown by illustrative examples how in the condition of erythraemia (which in the present stage of knowledge must be regarded as a neoplasm of erythroblastic tissue parallel to myelogenous leukaemia as a neoplasm of leucoblastic tissue) there may be complex and changing patterns of erythroblastic and leucoblastic activity. Thus erythraemia may co-exist with simple leucoblastic hyperactivity, i. e. leucocytosis. In other cases erythraemia may be associated with the presence of a few immature white cells, just as in myelogenous leukaemia a few immature red cells are invariably present. In cases such as that of Blumenthal there is a frank combination of the two sides of the marrow activity. Further, either condition may pass over into the other, permanently or as a temporary stage.

Blumenthal's case, with the excess of neutrophile myelocytes, suggests a case of ordinary myelogenous leukaemia—in which as a rule the neutrophil myelocytes are in excess—to which is added erythraemia. Cautley's case of erythraemia with leucocytosis and 93 per cent. of neutrophil polynuclears—can similarly be placed alongside Tuohy's case of neutrophil polynuclear leukaemia, and our own second case similarly falls into line alongside the cases of eosinophilic polynuclear leukaemia. In describing our second case we have adopted Di Guglielmo's term 'erythro-leukaemia' as a more truly descriptive title.

Minot and Buckman (1922), also Di Guglielmo, describe another type of marrow activity, which the latter has termed 'piastrinaemia' from the fact that, frequently in myelogenous leukaemia, and sometimes in erythraemia, megakaryocytes may be found in the peripheral blood, often, especially if in large numbers, associated with enormous numbers of blood-platelets. They suggest that accordingly as the erythroblastic or leucoblastic or platelet-forming tissues of the marrow are involved so we may have the blood picture of erythraemia, leukaemia, or (Di Guglielmo) piastrinaemia. The mixed picture of erythro-leukaemia is produced when both the erythroblastic and leucoblastic tissues play a part.

To this we would add from our study that in cases of leukaemia the leucoblastic activity may be further subdivided into (*a*) individual mature types, of which eosinophil and neutrophil examples are shown, (*b*) mixed mature types (eosinophil + polynuclear: Alexander), or (*c*) immature types (myelocytes), usually mixed. Clinically it is of interest to find that the leukaemia of mature cell types is just as fatal as that of the immature cell types, though much less common.

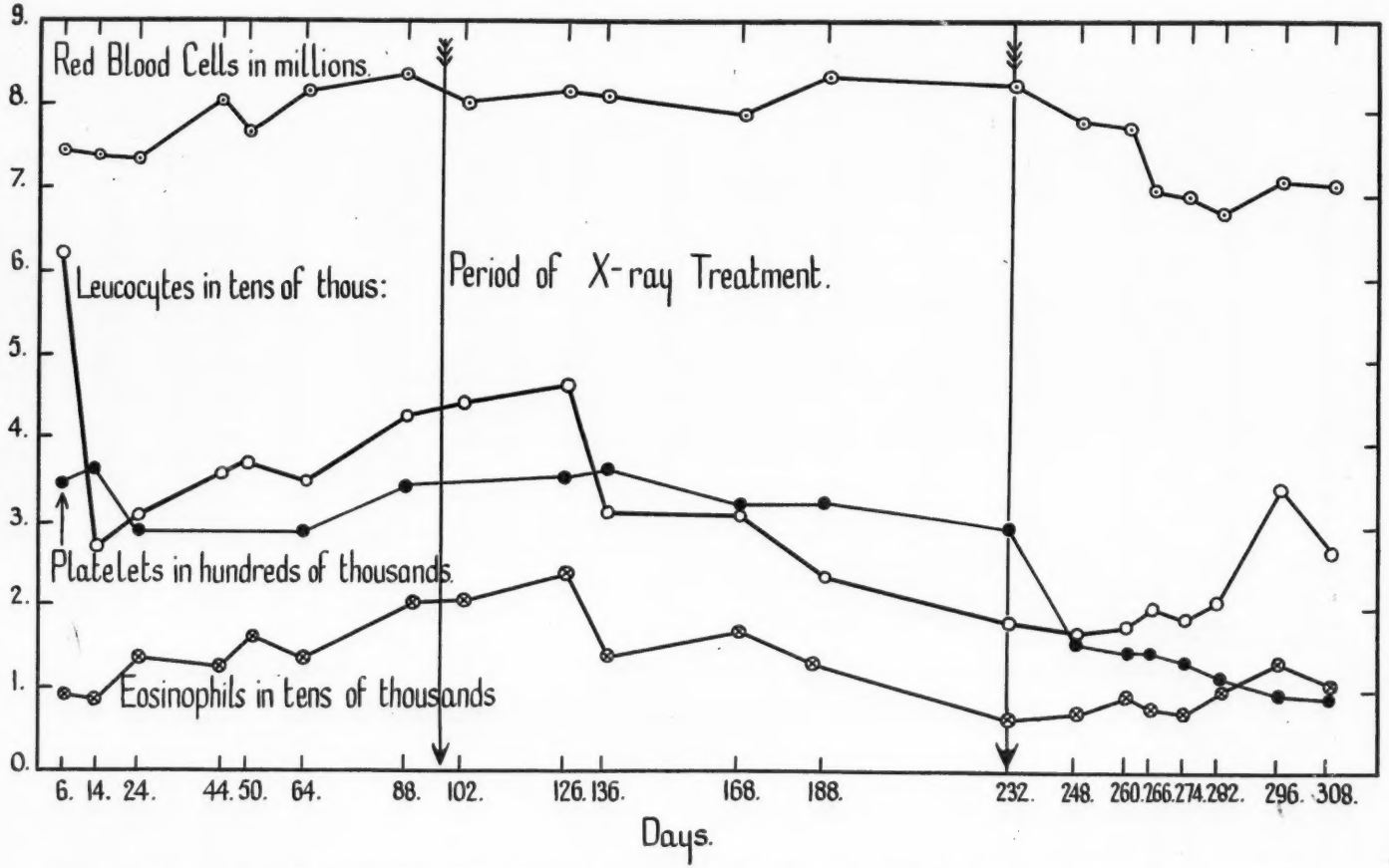
Further, in cases of erythraemia the same selective leucoblastic activity may be found—e. g. eosinophil (mature) erythro-leukaemia (Hay and Evans), neutrophilic (mature) erythro-leukaemia (Cautley), neutrophilic (immature)

erythro-leukaemia (Blumenthal). In conclusion, therefore, we hold that these are not separate and distinct diseases, but simply varying phases of marrow activity.

We would like to thank Dr. John Owen for permission to publish his case, and Drs. D. R. Evans and T. E. Jones for their help in obtaining the necropsy on Case I.

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Case II. M. R. Eosinophilic erythro-leukaemia. Showing the variations in the total red counts, platelet counts, total white counts, and total eosinophil counts.

TABLE I.

Blood Examinations of Case II, M. R., Eosinophilic Erythro-leukaemia.

	Total Blood Count.					Differential White Count (each based on 1,000 Leucocytes).								
Date.	H. B.	Reds.	Reticulocytes.	Whites.	Platelets.	Polymorphs.	Neut. myelocytes.	Basophils.	Basomyelocytes.	Eosinophils.	Lymphocytes.	Mononuclears.	Normoblasts per 1,000 Whites.	Megaloblasts per 1,000 Whites.
10.8.25	99	7,450,000	2·16	62,180	338,000	71·0	0	0·3	0	16·1	7·3	5·3	21	5
18.8.25	92	7,375,000	2·44	26,866	360,000	35·0	0·2	1·0	0·1	32·4	24·8	6·5	18	7
28.8.25	95	7,376,000	2·60	30,937	287,000	37·6	0	0·3	0	42·5	15·4	4·2	17	0
18.9.25	96	8,050,000	4·0	35,625	—	45·9	0	1·1	0	36·3	13·7	3·0	23	0
23.9.25	97	7,680,000	2·8	36,875	—	36·1	0	1·4	0	44·2	14·0	4·3	21	4
7.10.25	100	8,150,000	2·1	34,125	292,000	41·1	0·1	1·4	0	40·4	12·5	4·5	23	5
4.11.25	97	8,350,000	3·2	42,500	340,000	32·3	0·1	1·2	0	48·6	15·6	2·2	35	0
19.11.25	97	7,987,000	3·1	43,862	—	32·8	0·2	2·1	0	48·2	11·2	5·5	27	2
8.12.25	100	8,150,000	3·7	46,375	348,000	35·6	0·1	0·7	0	50·4	9·6	3·6	19	4
17.12.25	101	8,100,000	3·4	31,250	364,000	33·7	0·2	1·4	0·1	51·3	10·2	3·1	24	1
19.1.26	99	7,900,000	3·4	31,188	310,000	29·6	0·2	1·9	0	55·2	9·8	3·3	34	4
6.6.26	102	8,375,000	3·1	23,775	320,000	41·5	0·3	2·2	0·6	45·3	7·4	2·7	22	4
23.2.26	100	8,250,000	3·0	17,750	289,000	45·1	0·1	2·6	0·2	42·8	6·4	2·8	28	2
11.3.26	98	7,800,000	2·2	16,250	165,000	38·4	0·8	2·4	0	50·0	6·2	2·2	21	3
24.3.26	95	7,750,000	2·2	18,437	158,000	36·8	0·4	1·6	0·4	51·6	5·2	4·0	19	0
29.3.26	96	6,980,000	2·1	20,000	155,000	40·4	1·2	4·2	0·6	42·8	8·4	2·4	16	0
6.4.26	95	6,920,000	1·9	18,125	133,000	38·6	0·6	3·0	0·2	44·6	9·8	3·2	20	3
14.4.26	96	6,712,000	1·7	20,625	112,000	42·8	0·5	3·2	0·3	44·4	7·2	1·6	22	2
28.4.26	98	7,175,000	2·4	33,750	98,000	48·4	0·4	2·4	0	37·2	8·4	3·2	31	4
11.5.26	98	7,050,000	4·1	26,562	97,000	51·2	0·4	2·0	0	35·6	7·6	3·2	132	17

TABLE II.

Showing proportion of nuclear variety in cells containing eosinophil granulations. Case II. M. R. Eosinophilic Erythro-leukaemia. Each count based on 1,000 eosinophils.

Date.	Myelocytes.	Meta-myelocytes.	1 Lobe.	2 Lobes.	3 Lobes.	4 Lobes.
10.8.25	1·0	5·1	22·1	68·1	3·7	0
18.8.25	1·3	4·6	22·0	59·6	10·3	2·2
28.8.25	0·5	2·2	22·5	64·0	10·8	0
18.9.25	0·7	3·5	23·4	65·9	6·5	0
23.9.25	1·0	3·3	24·6	63·3	7·8	0
7.10.25	1·1	3·6	28·4	61·9	10·0	0
4.11.25	0·6	1·4	28·0	63·9	6·1	0
19.11.25	1·2	3·2	24·1	64·4	7·1	0
8.12.25	1·3	3·7	22·1	64·9	7·1	0·9
17.12.25	1·5	5·0	25·8	57·6	10·1	0
19.1.26	1·7	3·8	29·6	55·4	8·5	1·0
6.2.26	2·7	7·1	27·2	54·1	8·2	0·7
23.2.26	3·0	6·1	27·9	54·2	7·8	1·0
11.3.26	2·7	8·1	31·0	51·0	6·3	0·9
24.3.26	3·1	6·4	29·1	52·6	10·0	0
29.3.26	3·2	5·9	34·1	47·9	8·9	0
6.4.26	3·0	8·3	34·0	51·6	9·1	0
14.4.26	4·1	9·6	37·2	43·1	6·0	0
28.4.26	4·0	9·2	39·6	36·1	7·1	0·9
11.5.26	4·7	8·0	39·8	39·2	8·3	0

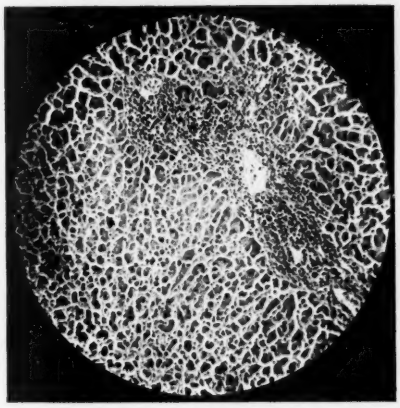


FIG. 1. Case 1. A.E. Acute eosinophilic leukaemia. Liver (×30) showing leukaemic infiltration. (Eosin and methylene blue.)

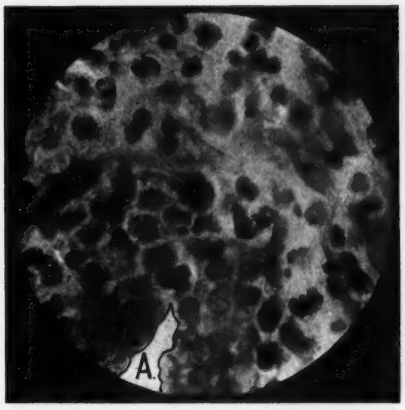


FIG. 2. Case 1. Liver (×1000) showing eosinophils. (Eosin and methylene blue.)
The letter A is placed in the lumen of a bile-duct.

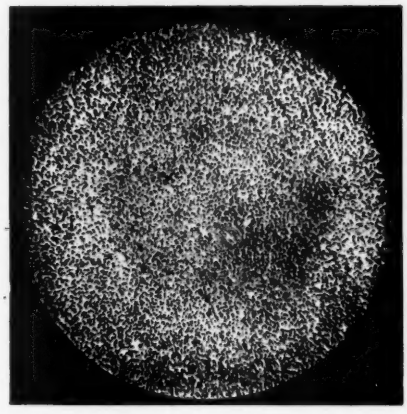


FIG. 3. Case 1. Spleen (×25) showing diffuse infiltration of a malpighian body with eosinophils. (Eosin and methylene blue.)

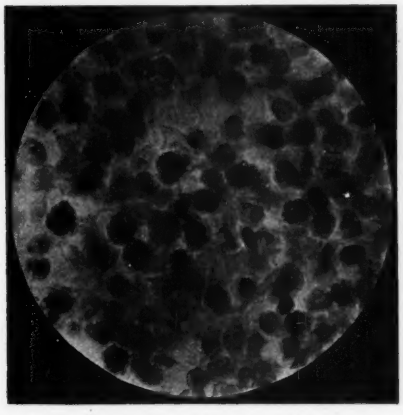


FIG. 4. Case 1. Spleen (×1000) showing the eosinophils in the pulp. (Eosin and methylene blue.)

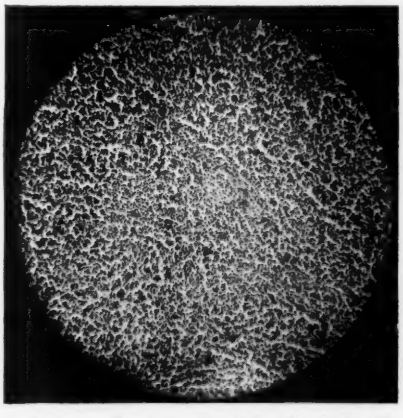


FIG. 5. Case 1. Lymph gland (×25) showing diffuse infiltration with eosinophils. (Eosin and methylene blue.)

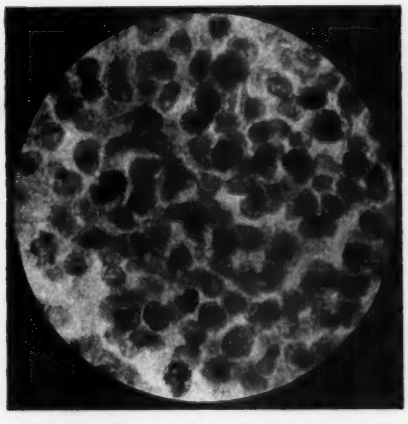


FIG. 6. Case 1. Lymph gland (×1000) showing the eosinophils. (Eosin and methylene blue.)

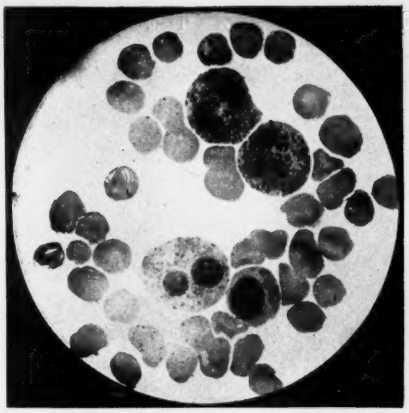


FIG. 7. Case 1. Blood film (× 1200) showing the variation in the size and number of the eosinophil granules. (Leishman.)

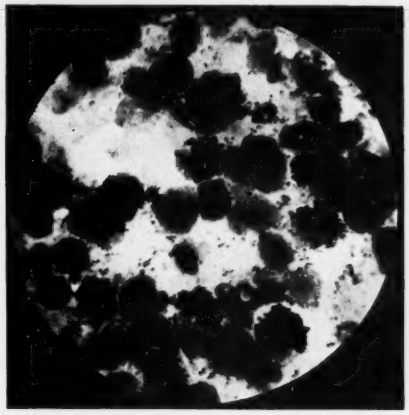


FIG. 8. Case 1. Smear of bone-marrow (× 1200) showing eosinophil myelocytes and polynuclears. (Leishman.)

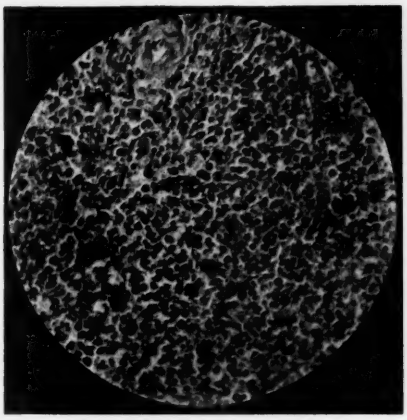


FIG. 9. Case 2. M.R. Eosinophilic erythroleukaemia spleen (× 200) showing infiltration of malpighian body with eosinophils. (Eosin and methylene blue.)



FIG. 10. Case 2. Spleen (× 1000) showing fibrosis of the pulp and eosinophilic infiltration. (Eosin and methylene blue.)

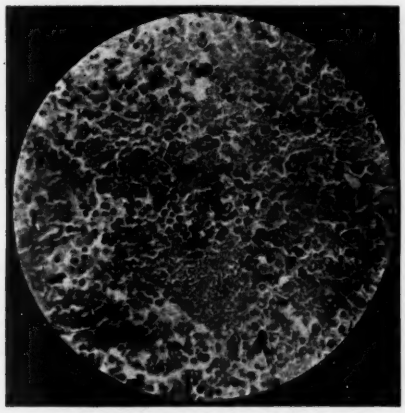


FIG. 11. Case 2. Marrow (× 200) showing congestion and cellular activity. (Eosin and methylene blue.)

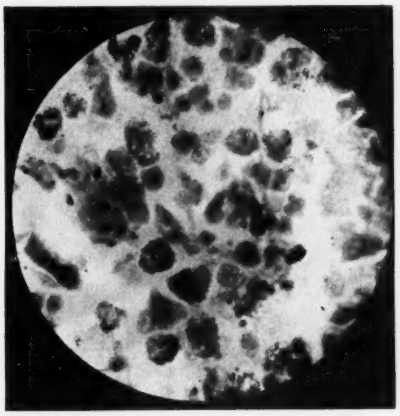


FIG. 12. Case 2. Marrow (× 1000) showing eosinophil myelocytes and polynuclears. (Eosin and methylene blue.)

IMPROVEMENT OF DIABETES IN A PREGNANT WOMAN DUE TO FOETAL INSULIN [1]

By R. D. LAWRENCE

(From the Pathological Department, King's College Hospital)

The use of insulin has stimulated fresh interest in the course of pregnancy in diabetic women because it has entirely changed the outlook both for the mother and the foetus. Adequate treatment of the disease with diet and insulin restores normal menstrual function to many women and an increasing number of pregnancies with successful terminations have been recorded in the last few years. These have been reviewed by Walker (1) in this country. Lambie (2) has also reviewed the previous literature on the subject, and readers are referred to these two works for further information.

Very few of these cases have been followed throughout pregnancy, so that little reliable information is available on the effect of pregnancy on the diabetic mother's carbohydrate tolerance. And no definite information has been gained on the interesting physiological question as to what extent, if at all, the development of foetal insulin production may help the mother. Experimental evidence on this latter point is contradictory, for while Carlson (3) and others produced evidence that foetal insulin may help the diabetic female, Allen (4) and, later, Macleod (5) and the Toronto workers were unable to corroborate this.

It has been possible to study the case recorded in this paper closely before, throughout, and after pregnancy. Clear evidence of foetal insulin aiding the mother has been obtained, and of a slight improvement in the mother's carbohydrate tolerance after as compared with before pregnancy. Studies are also included of the calorific requirements, the production of ketosis on different fatty acid/glucose ratios, and the complication of parenchymatous nephritis with oedema which appeared in the latter months.

History of the Case and Course of the Pregnancy.

The main facts of the case are shown in Table I.

Mrs. D. was married at the age of 27 in 1924, and about six months afterwards gradually developed diabetes mellitus. There was no hereditary nor familial history of diabetes and the patient had had no previous illnesses except colds. When first seen, in January 1925, she showed the usual symptoms of uncomplicated diabetes, the blood-sugar was over 0·3 per cent., and the urine

[1] Received August 18, 1928.

contained an abundance of sugar and acetone bodies and some protein. No casts were seen and the proteinuria disappeared completely when the diabetes was controlled by diet. She was treated as an out-patient and remained well and free from sugar until she broke her diet when on holiday at the end of 1925. After this she required insulin in doses varying from 5 to 15 units a day until the commencement of pregnancy. Throughout these two years the diet was kept constant at 40 C, 60 P, and 120 grm. of fat, and was on the whole fairly closely followed. In 1927 she asked if it were advisable to have a baby. As there was no family history of diabetes and the case seemed uncomplicated, the dangers and difficulties were pointed out to her and the choice left to herself.

Her last menstruation was on September 12, 1927, and she first came to see me again when she was *10 weeks* pregnant. She was suffering from considerable morning sickness and an increase of acetonuria was found. She had increased her insulin to 20 units a day and on this the blood-sugar was found to be normal (0·098 per cent.) four hours after the morning dose of insulin. But traces of sugar were frequently present in the urine and it seemed probable that the renal threshold had become lowered.

At the *16th week* she was admitted to King's College Hospital for a week of close observation. She had already increased her insulin to 26 units a day, as this seemed necessary in her opinion to keep the urine sugar-free or with only slight traces of sugar. The blood-sugar tests proved to be nearly always normal and the traces of sugar in the urine were due to lowering of the renal threshold to about 0·090 per cent. blood-sugar. A considerable amount of ketone bodies (usually about 1 grm. per day) was found in the urine, but there were no signs of clinical ketosis. The carbohydrate was raised to 60 grm. per day.

After a week in hospital, she continued to attend as an out-patient and remained in the same condition until the *25th week*, when the ankles began to be oedematous and slight traces of protein and a few granular casts were found in the urine. She was rested in hospital for 10 days, when the oedema diminished and the proteinuria completely disappeared, although the ketosis, a possible factor in the production of slight proteinuria, remained the same. For a few days the carbohydrate was increased to 80 grm. to reduce the ketosis, but the blood-sugar rose, although never above 0·200 per cent., and the insulin had to be increased to 36, and then to 44 units per day. Even this did not control the blood-sugar nor reduce the ketosis, which it seemed desirable to do. But it was felt that the carbohydrate would have to be raised to over 100 grm. a day and the insulin probably increased very largely to bring the blood-sugar down to normal. And it was thought, perhaps mistakenly, that with large carbohydrate meals and large doses of insulin the blood-sugar would swing from a high fasting to a low midday level and that the periods of hyperglycaemia might tend to produce hydramnios and a large foetus, whereas periods of hypoglycaemia might endanger the foetus in some unknown way. About this time the presence of twins was definitely established by X-rays.

The total calories had been kept low, only 1,600 and 1,680 at the 25th and 26th week respectively. It is difficult to know how many calories per kilogram this represents, as the rapid increase in weight from the 16th to the 25th week was mostly due to oedema. For purposes of calculating metabolism, her weight had been taken to remain constant until the later weeks of pregnancy, when allowance was made for the weight of the foetuses, the uterus, and placenta. At the *27th week* the diet was raised to 70 C, 67 P, and 135 grm. of fat, providing 32 calories per kilogram of body-weight. This was somewhat lower than the 35 calories per kilogram usually recommended for pregnant women. The fatty acid/glucose equivalent of this diet is 1·35 to 1 and higher still if we take into account the 30 grm. of sugar lost per day in the urine (see later). This ratio naturally produced a moderate degree of ketosis. However, the mother felt well, had no clinical signs of ketosis, and the CO_2 combining power of the plasma was 47 volumes per cent., a normal figure for a pregnant

woman. The foetuses also seemed active and growing, so that the total calories were deemed to be sufficient. Other tests at this time showed the mother to be in exact nitrogenous balance. Protein had disappeared from the urine, the blood urea was normal at 27 mg. per 100 c.c. and the blood cholesterol at 194 mg. per 100 c.c. It was felt that her condition was not entirely satisfactory in view of the ketosis and the somewhat raised blood-sugar level, but for reasons mentioned in the last paragraph she was discharged from hospital on the above diet and 44 units of insulin a day, feeling very well. She was in the same condition a few days later when examined as an out-patient.

When next examined, at the *28th and 29th weeks*, a striking change had taken place in her carbohydrate metabolism. The blood-sugars had fallen to a low normal level, both fasting and after food. It was possible to reduce the insulin considerably and to add 10 grm. carbohydrate to the diet. The possibility of foetal insulin aiding the mother was at once thought of. Therefore, although it might have been advisable to give more carbohydrate in view of the ketosis, the carbohydrate was kept constant at 80 grm. a day and the insulin was reduced, because it is more satisfactory to estimate an improvement of tolerance by keeping the diet constant and reducing the insulin. By the *33rd week*, 18 units was sufficient to maintain entirely normal blood-sugars and even produce occasional symptoms of hypoglycaemia. I do not feel certain that the attacks of maternal hypoglycaemia had any effect on the foetuses, but the mother was under the impression that they were definitely more active at these times. An attempt was made to omit the insulin altogether, but after three days the blood-sugar had risen to 0·137 per cent. fasting and after a week to 0·202 per cent. Three hours after meals the blood-sugar was lower than these fasting levels, a common occurrence in diabetics who are not having insulin, and apparently due to stimulation of endogenous insulin by the carbohydrate of the first meal. The ketone excretion remained at about ½ to 1 grm. per day and the CO_2 combining power of the plasma was 48·7 per cent. However, as the blood-sugars were not quite normal without insulin, its use was recommenced in doses of 14 units a day. By this time oedema of the legs, the vulva, and the lower part of the abdominal wall was very extreme and the patient was readmitted to hospital on 15.5.28 for rest in bed and closer observation. Complete urinary and other studies of metabolism were commenced from May 17, and are shown in Table II. They will be discussed in more detail later.

From the *35th week* onwards the difficulties that arose were due not to the control of the diabetes but to the extreme oedema which appeared to be due to a complicating parenchymatous nephritis. Rest in bed and elevation of the feet made no appreciable difference to her condition and only caused some of the fluid to run from the lower extremities into the face and the back. An attempt was made to reduce the oedema by diuretin and urea, but this only caused vomiting. Oedema of the vulva was so great that it was obvious that labour could not take place in the ordinary way, and for this reason a Caesarean section was judged to be necessary by Drs. Gilliatt and Palmer. Small amounts of protein and some granular casts were now constantly present in the urine, although there was no evidence of nitrogen retention from the amounts of urea in the blood and urine. It was discovered that the salt excretion in the urine was extremely small (about 1–2 grm. a day) and this pointed to a salt retention in the tissues as the real cause of the oedema, augmented no doubt by increased intra-abdominal pressure. Preparatory to the Caesarean section and the probable necessity of a general anaesthetic, further investigations were undertaken on May 22 and showed a considerable fall in the alkali reserve to 35 volumes per cent., although the ketone excretion was, if anything, somewhat less than earlier in the pregnancy. The blood chlorides were found to be at the highest levels given in the text-books as normal, 620 mg. per 100 c.c. in plasma, and 490 mg. in the whole blood. The blood urea had risen to 43 mg. per 100 c.c.

In order to raise the low alkali reserve, phosphates were given by mouth

and the carbohydrate was raised to 110 grm., making a fatty acid/glucose ratio of 0·93/1. After three days ketone bodies were entirely absent from the blood and urine, and when the carbohydrate was raised to 140 grm. a day the blood-sugar still remained entirely normal. After a week the alkali reserve had risen to normal, 46 volumes per cent., and the blood urea had fallen to 20 mg. and the blood chlorides to 550 mg. (see Table II). However, the blood cholesterol had risen to 258 mg. per 100 c.c., the urinary chloride excretion remained very low, the proteinuria and casts were increasingly abundant, and the oedema no better. Mr. Palmer, therefore, decided to perform a Caesarean section at once at the *37½ week*.

Caesarean Section. This was performed at 10.30 p.m. The usual insulin and the usual diet in easily digested form were given during the day. The blood-sugar immediately before operation was 0·120 per cent., and after half an hour of open ether anaesthesia had risen to 0·150 per cent. This was taken at the moment when the babies' cords were ligatured and blood was at once collected from them with a syringe to obtain a simultaneous comparison of maternal and foetal blood. The amniotic fluid seemed normal in amount. The babies were normal but of different sex, and of very different size—a boy of 8 lb. 6 oz. and a girl of 4 lb. 10 oz., making a total weight of 13 lb., about the average combined weight of twins. This difference appeared to be due entirely to an unequal division of placental nourishment. Their blood-sugar was considerably lower than the mother's—0·086 and 0·068 per cent. from the respective cords. Unfortunately the cords were mixed and it is not known whether the larger child had the higher or lower blood-sugar. These figures are low for newborn infants—one is definitely hypoglycaemic—and perhaps may be taken as suggestive of excessive production of foetal insulin. At any rate, by comparison with the mother's (0·150 per cent.), they show definite insulin production on the foetuses' part. The mother underwent the operation quite normally and the Fallopian tubes were partially resected to prevent further pregnancies.

Next morning the mother's fasting blood-sugar was somewhat elevated at 0·160 per cent., but fell to the usual level of 0·098 per cent. four hours after her usual insulin. However, she was unable to eat much food for the next two days, perhaps only half the usual carbohydrate, and the blood-sugar remained normal and the urine sugar and acetone free. On the third day she resumed her previous full diet of 140 grm. carbohydrate and the previous insulin quite failed to keep the blood-sugar normal, so that the insulin had to be rapidly increased. Ten days after labour she required 44 units a day to reduce the blood-sugar to normal and the fasting level in the morning became high—0·278 and 0·231 per cent. on two occasions. This showed that she had relapsed considerably in comparison with her condition before labour. The puerperium and the healing of the womb were normal and she got up on the fourteenth day after the Caesarean section. The protein in the urine rapidly diminished and casts became infrequent, but a trace of albuminuria was still present three weeks after labour. The oedema had completely disappeared five days after labour, and this was accompanied by a large diuresis. When she was able to be weighed she was found to have fallen from 179 lb. before labour to 116 lb. after, which is 9lb. less than when pregnancy commenced. She was very anaemic, with a red count of 2 million cells and haemoglobin of 40 per cent., giving a curiously high colour index of 1. The red cells had risen to 3 million after a week's treatment with iron and a higher protein diet. For a few days she secreted a certain amount of milk from the breasts and one of the babies was put to the breast, which I had not intended. She secreted about 12 oz. of milk for three days. It was intended to analyse this, but on the day when samples were to be collected the milk dried up almost completely. Only sufficient was obtained to estimate the protein, which was normal at 1·5 per cent. When the anaemia was discovered any further attempt to suckle the baby was forbidden. The progress of the babies on artificial feeding was satisfactory. They passed no sugar in the

urine. They showed no signs of hypoglycaemia. No subsequent estimation of their blood-sugars was made.

For four days before leaving hospital the mother was put back on the same diet as she was on before her pregnancy—40 C, 60 P, and 120 grm. fat. Her insulin requirements were worked out afresh and she was found to need less insulin than before pregnancy. Sixteen units a day produced slight hypoglycaemia at a blood-sugar level of 0·063 per cent. four hours after the morning dose of insulin, although the fasting level was high, 0·201 per cent. Indeed, 12 units after pregnancy seemed equivalent to 18 units before. If low blood-sugars rest the pancreas and improve endogenous insulin production, it is not surprising to find her tolerance improved, because, by the aid of foetal insulin, she had lived at a low normal blood-sugar level for ten weeks before labour.

Her diet was raised considerably to 55 C, 82 P, and 165 fat, and she was discharged from hospital feeling well and able to look after her babies. She gained 6 lb. in weight during the next week. However, she rapidly developed a breast abscess and allowed it to become very large before she reported at hospital. She returned in almost a precomatose condition, with a blood-sugar of 0·4 per cent. and a very heavy ketosis. The abscess was opened, large doses of insulin were given, and she was found to require 60 units a day. As the abscess healed it was possible to reduce the insulin to 28 units a day; she rapidly regained her weight and strength and was discharged home after her many vicissitudes.

Occasional traces of protein and a few hyaline casts were present in the urine during the period of sepsis, and had not completely disappeared by the 10th week after delivery.

Detailed Metabolic Studies.

For two weeks before, and three weeks after, delivery, the various urinary constituents were estimated quantitatively every day. I am greatly indebted to Mr. F. A. Mann, of the Pathological Department, Maudsley Hospital, for these detailed analyses. The results obtained are given in Table II and seem of sufficient interest to merit closer attention. The diet, insulin, and blood-sugar figures over this period may be gathered from Table I.

Evidence of parenchymatous nephritis. Estimations of the total chloride excretion at once gave the explanation of the oedema which was so severe from the 34th week to the termination of pregnancy. She rarely excreted more than 2 grm. of salt a day, although eating an average amount in her diet. The blood chlorides were found to be at the extreme high limit of normal figures. No doubt the oedema of the legs and vulva was accentuated by the increased intra-abdominal pressure, but it depended primarily on salt retention in the tissues. This degree of salt retention seemed out of all proportion to the slight degree of renal damage which the other tests showed to be present. When the diabetes was first discovered, in 1925, some albumin, but no casts, was found in the urine. No proteinuria was found again until the 25th week of pregnancy when only traces and occasional hyaline and granular casts were discovered. These disappeared on rest in bed. Throughout pregnancy the proteinuria was very slight until the last few days, and indeed was often entirely absent even as late as the 35th week. There was never any evidence of

nitrogen retention and the blood-pressure remained normal. The blood cholesterol, which had been normal throughout and after pregnancy, was found to have risen to the high figure of 258 mg. per 100 c.c. on the day before delivery, when the amount of protein in the urine was also greatly increased. This suggests the type of nephritis which receives the name of 'nephrosis' in the American literature. The oliguria which preceded labour was succeeded by a copious polyuria by the fourth day after labour, the first on which it was possible to obtain a complete collection of the urine, and for a few days the chloride excretion was increased much above the normal. In other words, the salt retention rapidly disappeared and with it all signs of oedema. How great the water retention had been can be seen by the difference in weight before and after labour. When allowance is made for the weight of the foetuses, the uterus and placenta, the change in weight from 176 to 116 lb. represents a retention in the tissues of over 20 litres of water. Occasional slight traces of protein and a few hyaline casts were still present in the urine ten weeks after labour.

On the whole, it seems reasonable to suggest that the oedema and salt retention was not due entirely to kidney inefficiency or intra-abdominal pressure, but was primarily a retention of water by the tissues. Fischer maintains that this can be brought about in conditions of acidity (or at least changed acid/alkali balance) by an increased affinity of the tissue colloids for water. Our patient had certainly suffered from ketosis for some months and it is at least possible that this was a factor in the retention of water by the tissues.

Evidence of acidosis. Although considerable ketosis had been present from the 16th to the 36th week, about ½ to 1 grm. total ketonuria per day, no clinical signs of acidosis were ever observed. The alkali reserve also remained normal for a pregnant woman, in whom the CO_2 combining power of the blood tends to be 10 volumes per cent. lower than in non-pregnant women. The urinary studies which commenced at the 35th week showed slight but definite evidence of acidosis. The pH of the urine remained constantly at a low figure and the total acidity and the ammonia coefficient slightly above normal. The total excretion of phosphorus between May 17 and 22 was definitely reduced, showing that the prolonged slight acidosis had produced a phosphate exhaustion. On May 22 the alkali reserve was found for the first time to be definitely subnormal at 35 volumes per cent., although no change had been made in her diet, nor its fatty acid/glucose ratio of 1·15 to 1. This ratio was at once raised to 0·93/1 by the addition of 30 grm. of carbohydrate to the diet and alkaline phosphate was given by mouth (6 grm. per day). Three days later all ketone bodies had disappeared from the blood and urine and the phosphate excretion and the urinary pH began to rise. But the pH of the urine, the total acidity, and the ammonia coefficient still remained on the acid side. These changes in acid/alkali balance made no appreciable difference to the chloride retention or the oedema, and the proteinuria increased daily in amount.

After labour no more phosphate was given by mouth. During the period of polyuria the urinary pH became more normal, but returned later to figures on the acid side, although ketosis remained absent. Considerable quantitative variations in the urinary constituents occurred during this time, and their significance, if any, is not understood.

Protein requirements and nitrogenous balance. Before pregnancy and up to the 35th week the diet provided about 1·1 to 1·2 grm. of protein per kilogram of body-weight. At the 26th week the patient was excreting an average of 9·3 grm. of nitrogen on a diet containing 60 grm. of protein (9·6 grm. of nitrogen) so that the nitrogen balance was slightly positive. At the 35th week (see Table II) the nitrogen balance was for the most part still slightly positive, although it became negative on occasional days. When more carbohydrate was added to the diet, its usual effect in sparing protein and reducing nitrogenous excretion was seen, and the balance became positive to the extent of some 5–7 grm. a day until the end of pregnancy. During the diuresis that succeeded delivery, a large excess of nitrogen was occasionally washed out. When it was discovered that the patient had considerable secondary anaemia, it was thought advisable to give her more protein (105 grm. a day), and after this the balance remained positive to the extent of 5–6 grm. a day. It is said that a pregnant woman requires about 1·5 grm. of protein per kilogram of body-weight, but our patient seemed to maintain a positive nitrogen balance on less than this.

Discussion.

Improvement in tolerance and relapse after labour. The great improvement in carbohydrate tolerance from the 28th week of pregnancy onwards is the most striking feature of this case. Up till then her tolerance had decreased. A comparison of her condition at the 27th week with 44 units of insulin a day shows no appreciable difference from that at the 34th week when no insulin was being given. And a comparison of her condition before and in the last week of pregnancy shows a gain in carbohydrate tolerance of 100 grm. with more normal blood-sugars than before pregnancy. From the low level of the blood-sugar there seems little doubt that still more carbohydrate could have been adequately tolerated. It was noticeable in the last few weeks that each addition of carbohydrate raised the maternal blood-sugar for a day, after which it became normal again, suggesting an increased insulin response by the foetuses to a temporarily raised maternal blood-sugar. The necessity of terminating the pregnancy prevented an attempt to see how far the carbohydrate could be increased. And it is doubtful if such an attempt would have been advisable, as the foetuses would probably have developed excessive insulin function and become oversized. The increasing development of foetal insulin seems the only possible explanation of the mother's improvement, and it is to be noted that it took place at the time when the foetal pancreas first becomes functionally developed. The relapse after delivery, when she required more insulin again on a constant diet, is further

proof of the intervention of foetal insulin. This appears to be the first case in the literature in which this fact has been clearly established, and may be due to the accentuation of the effect from the presence of twins.

It is interesting to note that her tolerance had improved during pregnancy, as shown by the fact that she required less insulin after than before pregnancy, on the same diet. One might expect such an improvement in pancreatic function from living as she had done for ten weeks at a low blood-sugar level. Unfortunately it was impossible to observe if this improvement was maintained, because the complication of a large breast abscess produced a great deterioration in her condition and raised the insulin requirements for a time to 60 units a day.

Calorific value of the diet. Before pregnancy the patient maintained weight and energy on a fairly low diet of 28 calories per kilogram of body-weight (1,520 calories). Throughout pregnancy the diet was kept lower than is generally supposed to be necessary for pregnant women, a figure given as about 35 calories per kg. On account of the large gain in weight due to oedema and water retention it is difficult to know what figure to take for purposes of calorific calculations. Towards the end of pregnancy calculations have been made not from her actual weight (179 lb.) but from the weight immediately after delivery, when the oedema had disappeared, plus the weight of the foetuses, uterus, and placenta. This probably gives the best idea of the calories she was receiving per kg., although it is impossible to gauge what inaccuracies the neglect of the dropsical fluid must involve. Table I shows that during most of the pregnancy she was receiving 30 calories per kg. and it was only in the last week that this was raised to 34·6. The energy and well-being of the mother (before she became water-logged with oedema), the normal activity and development of the foetuses, and the positive nitrogen balance were taken as evidence throughout pregnancy that sufficient total calories were being provided. However, it was obvious after labour that she had lost considerable weight (9 lb.) during pregnancy and that she had become very anaemic. It is possible that these features were partly caused by undernutrition and might have been avoided by a more liberal diet. But the kidney complications masked her loss of weight and complicated an appreciation of her condition. I regret that I did not follow her blood count throughout the pregnancy. There was, however, no suggestion of anaemia from the mere appearance of the blood collected for other tests until ten days before delivery, when it became obviously watery and anaemic. It is of course possible that the developing anaemia was an accompaniment of the increasing degree of nephritis and not in any way due to undernutrition.

Ketosis and the fatty acid/glucose ratio. Before pregnancy the patient tolerated a high fat diet well and excreted only traces of acetone on a fatty acid/glucose ratio of 1·56/1. By the 10th week of pregnancy more acetone had appeared in the urine on the same ratio and remained nearly constant between half and one gramme a day till near the end of pregnancy. But from the 10th week onwards the fatty acid and glucose equivalents of the diet cannot be

taken as an index of the actual amounts of these substances metabolized. For the loss of food from morning sickness and the loss of glucose from the lowered renal threshold, and later from the carbohydrate 'drain' of the foetus, have all to be taken into account. At the 27th week the fatty acid/glucose ratio of the diet was 1·27/1, but when allowance is made for the 30 grm. of sugar excreted per day owing to the lowered threshold, the ratio becomes 1·65/1, on which we might expect considerable ketosis. For the next few weeks the exact ratio is not known, because, although the diet was accurately followed, varying amounts of sugar were lost in the urine and were not estimated. At the 35th week, when the renal threshold had become normal and the urine sugar-free, a considerable ketosis was still present on a ratio of 1·15/1 in the diet. But by this time the additional factor of the carbohydrate 'drain' of the foetuses from the mother had become important and must be reckoned with. This carbohydrate 'drain' has been estimated at some 50 grm. of glucose a day (see Lambie, loc. cit.), and when this figure is subtracted from the glucose of the diet—and the drain is likely to be more than this in the case of twins—the fatty acid/glucose ratio becomes 1·8/1 on which we would expect ketosis. In the 36th week the carbohydrate of the diet had been raised to 110 grm. per day and then for the first time during the pregnancy ketonuria completely disappeared. This is an apparent ratio of 0·93/1, or an actual ratio, allowing for the drain, of 1·33/1, which ought to abolish ketosis. These rough calculations indicate that there was no important change in the ketogenic-antiketogenic ratio tolerated throughout pregnancy when the above allowances are made. Before pregnancy the patient was not entirely free from ketosis on a ratio of 1·56/1, and throughout pregnancy had considerable ketosis on ratios of 1·65/1 and 1·8/1, but none on a 1·33/1 ratio. Therefore it would appear that there is no inherent tendency for pregnancy to disturb the toleration of fat and the usual ketogenic-antiketogenic balance when the complicating factors of sickness in the early months, perhaps loss of glucose from a lowered renal threshold and the foetal carbohydrate 'drain' in the latter months are taken into account.

Lowered renal threshold. It is of interest to note the time of appearance and disappearance of the lowered renal threshold, the renal glycosuria of pregnancy, in this case. By the 16th week the threshold was definitely proved to be lowered to about 0·09 blood-sugar. Urinary tests suggest that it may have been lowered as early as the 10th week, but the patient was not closely enough observed to be quite certain of this. It remained low until the 33rd week, but was clearly ascertained to have become normal again at the 34th week. It is common enough to find the renal glycosuria of pregnancy appear and disappear at any time during pregnancy. But it is more usual for it, in my experience, to disappear only after labour.

Summary.

The course of a twin pregnancy in a diabetic woman is described and the following facts established:

1. Up to the 27th week of pregnancy the mother's carbohydrate tolerance deteriorated. From the 28th week until the end of pregnancy a great improvement, to the extent of at least 100 grm. of carbohydrate a day, took place. This increase in tolerance was not maintained after labour. It can therefore be ascribed only to foetal insulin aiding the diabetic mother.

2. The mother's carbohydrate tolerance was slightly greater after than before pregnancy.

3. A lowering of the renal threshold took place at the 16th week, but it returned to normal again at the 34th week.

4. No increase in the ketosis or change in the fatty acid/glucose ratio tolerated was observed when the loss of glucose, due to the lowered renal threshold in the early months and to the carbohydrate 'drain' of the foetuses in the later months, is taken into account.

5. The pregnancy was complicated in the later months by severe oedema due to salt retention and parenchymatous nephritis. This necessitated a Caesarean section by which two healthy twins were delivered.

It is a great pleasure to express my indebtedness to Dr. Gilliatt and Mr. Palmer for their advice and aid in the obstetrical direction of the case; also to Dr. Olive Buckley, Mr. F. A. Mann, and Mr. H. R. Miller for help in so many of the investigations.

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TABLE I.

Date.	Weeks.	Urine. Sugar.	Urine. Ketones.	Urine. Albumin.	Blood-sugar.	Diet.	Cals. per Kgm.	Ins.	Weight Lbs.	Remarks.
2.1.25	—	+ + +	R. +	+	325	40 C., 60 P., 120 F.	28	0	122	Diabetes discovered
12.2.25	—	0	0	0	128	,,	—	0	120	—
6.10.25	—	+ + +	R. + + +	0	258	,,	—	—	115	Broke diet
14.12.25	—	0	0	0	—	,,	—	15	—	Insulin commenced
7.12.26	—	0–tr.	0–tr.	0	—	—	—	14	125	—
12.9.27	1	0–tr.	R. tr.	0	—	,,	—	18	125	Last menstruation
17.11.27	10	0–tr.	R. + +	0	98	,,	—	20	—	Morning sickness
4.1.28	16	sl. tr.	R. + + +	0	*153* 80	60 C., 60 P., 120 F.	—	26	124	Renal threshold at 0·09 %
5.3.28	25	+	F. sl. tr.	tr. few casts	*127* 123	,,	29	26	140 (125)	Oedema of ankles
10.3.28	26	+ +	R. + + +	0	*190* 161	80 C., 60 P., 120 F.	30	36	(125)	Twins. X-ray diagnosis
23.3.28	27½	30 grm.	R. + +	0	*157* 166	70 C., 67 P., 135 F.	32	44	138½	—
30.3.28	28⅔	trace	F. tr.	sl. tr.	*113* 108	,,	—	44	—	—
13.4.28	30½	trace	R. + +	0	*123* 88	80 C., 67 P., 135 F.	—	36	152	Marked oedema
20.4.28	31½	sl. tr.	R. +	0–sl. tr.	*104* 78	,,	—	26	—	—
4.5.28	33⅓	sl. tr.	R. + +	sl. tr.	*109* 113	,,	—	18	—	—
11.5.28	34½	sl. tr.	R. + +	trace	*202* 173	—	—	0	—	Renal threshold normal
17.5.28	35½	0	R. + + +	0	*108* 103	80 C., 75 P., 135 F.	30·1	14	179 (132)	—
24.5.28	36½	0	0	+	*100* 79	110 C., 75 P., 135 F.	32	18	—	—
29.5.28	37	0	0	+ +	*101* 107	140 C., 87 P., 135 F.	34·6	18	175 (132)	—
30.5.28	—	0	0	+ + casts +	101	,,	—	18	—	Caesarean section
31.5.28	—	0	0	—	*161* 98	?50 C. ,,	—	18	—	—
1.6.28	—	0	0	+ + casts	98	?55 C. ,,	—	18	—	—
2.6.28	—	+	0	trace	203	140 C. ,,	39·2	18	—	—
6.6.28	—	trace	0	trace	*178* 128	140 C. ,,	39·2	42	—	2 million R. B. cells
9.6.28	—	trace	0	sl. tr.	*278* 143	140 C., 105 P., 150 F.	39·2	44	—	3 ,, ,, ,,
21.6.28	—	0	0	sl. tr.	*201* 63	40 C., 60 P., 120 F.	29	16	116	—
10.7.28	—	+ +	sl. tr.	0–sl. tr.	—	55 C., 82 P., 165 F.	40	60	107	Breast abscess, 3.7.28
27.7.28	—	0	0	sl. tr.	143	,,	40	28	117	3·6 million R. B. cells

Table I shows the condition of the carbohydrate metabolism at various periods. Urine tests: tr. = trace, sl. = slight, + + + = 1·5 % of sugar or more: R. = Rothera's test: F. = Ferric chloride. Blood-sugar in milligrams per 100 c.c.; those italicized are fasting blood-sugars; the rest 4 hours after the morning dose of insulin. For further description see text.

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TABLE II.

Date. 1928:	17.5.	21.5.	22.5.	25.5.	30.5.	4.6.	5.6.	8.6.	13.6.	20.6.	Normal Figures.
Urine, c.c. per day	1063	1270	785	1880	950	3160	2450	2150	1380	1565	1500
pH	4·9	4·9	4·9	5·4	5·1	5·8	6·9	6·0	5·5	5·3	6·0
Ketones, grm.	0·61	1·4	0·7	0	0	0	0	0	0	0	0
Total acidity, c.c. N/10	400	467	311	429	452	423	127	559	519	407	350
NH_4 and amino acid N., grm.	0·577	0·571	0·400	0·669	0·729	0·920	0·380	0·795	0·636	0·447	0·700
N. output, grm.	9·08	12·71	7·80	7·91	8·91	16·39	9·26	7·44	13·52	12·93	—
N. balance, grm.	2·92	−0·71	5·15	5·04	4·99	−2·49	4·64	11·26	5·28	5·77	—
NH_4 coefficient, %	6·36	4·48	5·14	5·5	7·25	5·68	4·10	10·7	4·7	3·45	2–5
Phosphorus, grm.	0·702	0·927	0·542	1·053	0·950	0·718	0·586	1·07	1·41	1·04	1·0
Total chlorides, grm.	1·49	0·76	1·18	4·14	1·9	15·8	16·7	11·6	7·2	3·76	8–12
Protein	0	trace	+	+	+ + +	trace	trace	trace	trace	sl. tr.	—
Blood.											
Urea, mg. per 100 c.c.	42	—	—	—	20	—	—	—	—	—	18–45
Chlorides, blood, mg. per 100 c.c.	—	—	490	—	460	—	—	—	—	460	450–500
„ plasma, mg. per 100 c.c.	—	—	620	—	550	—	—	—	—	540	560–620
Cholesterol, mg. per 100 c.c.	152	—	—	—	258	—	—	—	—	176	140–190
Alk. reserve (vols. CO_2)	(on 11th)	—	—	—	—	—	—	—	—	—	—
Plasma (vols. CO_2)	48	—	35	—	46	—	—	—	—	59·9	55–75
Whole blood (vols. CO_2)	—	—	33	—	—	—	—	—	—	56·3	—
Carbohydrate, grm.	80	80	110	110	140 (5 days)	140	140	140	140	40 (1 day)	—

Table II shows representative figures from the quantitative analyses which were carried out daily for 5 weeks. The double line represents the Caesarean section and the last column shows what are average normal figures. For full description see text.

A NEW TEST OF RENAL FUNCTION[1]

By R. T. BRAIN and H. D. KAY
(From the Medical Unit, The London Hospital)

None of the tests of renal function hitherto described can be said to give a completely satisfactory estimate of the extent of renal damage. In fact, it is unlikely that any test will be devised which will register the effects of renal disease and these effects alone, and will not be influenced by extra-renal factors (vide (1)).

In the light of some recent work on renal excretion of phosphate, it appeared to us that a test founded on the enzymic activity of the kidney might approach a little more closely to the ideal. In 1925 Eichholtz, Robison, and Brull (2), from experiments on the heart-lung-kidney preparation, had put forward the suggestion that the inorganic phosphate of the urine was derived from the phosphoric esters of the plasma, these esters being hydrolysed by the very active phosphatase known to be present in kidney tissue. One of the present authors (3) had found that the phosphatase content of kidney tissue varied, during the life-history of the animal, with the activity of the kidney as an excretory organ, the embryonic kidney having very little phosphatase, whilst the maximum value per gramme of renal tissue was not attained till some days after birth (rabbit). It was very shortly afterwards observed by us (4) that both in chronic nephritis in man and in acute experimental nephritis in rabbits the phosphatase content of the kidney was much diminished, the fall in enzymic activity running parallel with the degree of structural damage revealed histologically. It seemed that the extent of this damage in patients with nephritis might be disclosed by artificially raising the phosphoric ester content of the plasma by a standard amount, and observing the quantity of additional inorganic phosphate excreted subsequently in the urine, as compared with that excreted following the same stimulus in the urine of a normal individual.

In experiments on certain factors controlling phosphate excretion we have found in collaboration with P. G. Marshall (5) that a perfectly safe and certain method is available for producing an artificial increase in the phosphoric esters of the plasma, namely the intravenous injection of sodium glycerophosphate. This phosphoric ester is readily hydrolysed by the phosphatase of kidney tissue, is inexpensive, easily obtained in a relatively pure form, and may be sterilized

[1] Received for publication 11 August 1928.

without decomposition. It is very soluble[2] in water, so that a large quantity of organic phosphorus may be administered from a small syringe. Five grammes of the solid dissolved in water and made up to 10 c.c. was found to be a convenient dose for intravenous injection, producing in normal individuals and in nephritics an appreciable rise both in the ester phosphorus of the plasma[3] and also in the urinary phosphorus.

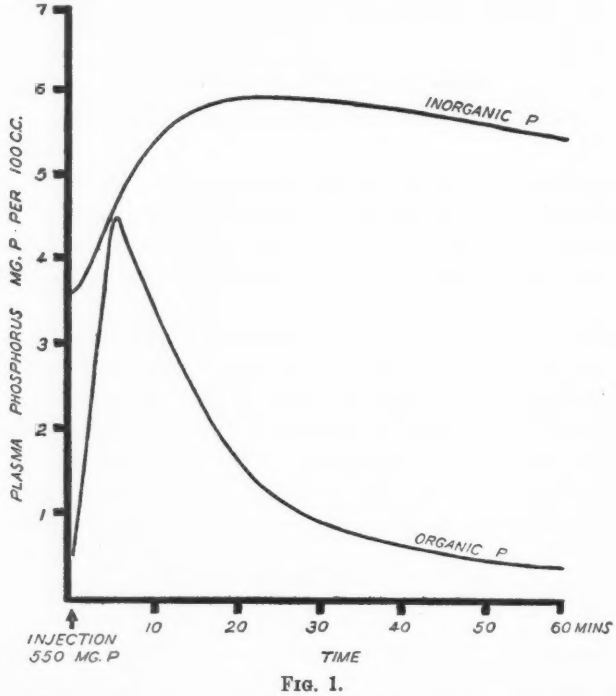


FIG. 1.

The effects of such an injection on the plasma inorganic and ester phosphorus are shown in Figs. 1 and 2. The curves in Fig. 1 are derived from 33 observations on normal subjects, in Fig. 2 from 42 observations on patients with nephritis. The inorganic phosphate curve is higher in nephritic patients than in normals, and the rate of disappearance of organic phosphate from the plasma rather slower. The difficulty of excretion of both organic and inorganic phosphate by the damaged kidney is responsible for these differences.

Preliminary experiments revealed that much of the glycerophosphate administered was excreted as organic phosphate during the hour following the injection. There was also an increase in the rate of excretion of inorganic phosphate during this period in all the normal individuals and in the majority

[2] The solubility of neutral sodium glycerophosphate far exceeds that of the inorganic sodium phosphates.

[3] If given by mouth, sodium glycerophosphate appears to be completely hydrolysed before absorption. An increase in the inorganic phosphate of the plasma is observed, but no rise in the ester phosphorus (5).

of the patients with nephritis. Comparison between normals and nephritics showed, however, marked differences in the rate of phosphate excretion between the two classes.

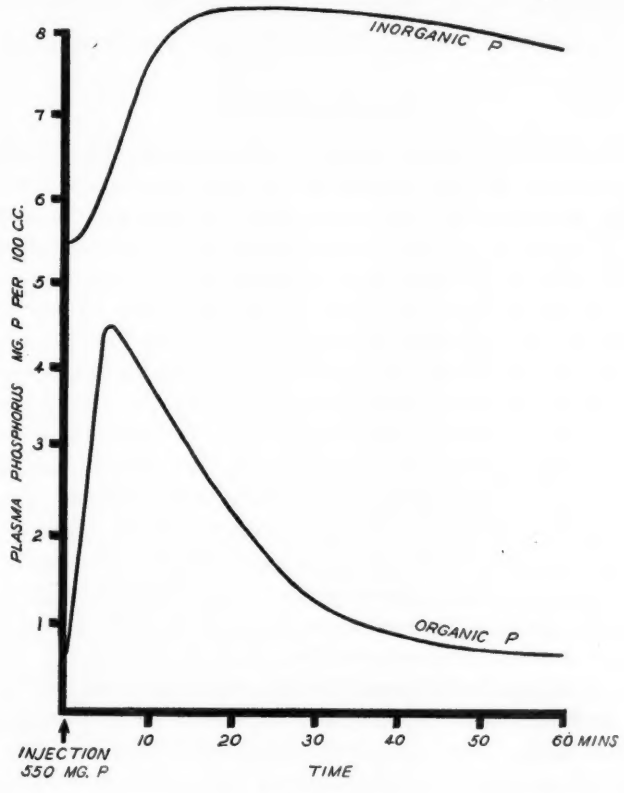


FIG. 2.

It was at this stage that evidence from various directions led us to suspect (5) that the suggestion of Eichholtz, Robison, and Brull was not true for the intact animal, and that therefore the theoretical basis on which our new test had been founded was insecure. Nevertheless, we were obtaining such satisfactory agreement between the amount of extra urinary phosphorus excretion during the hour following the injection and the clinical findings with regard to the probable degree of renal involvement in cases of chronic and acute nephritis that we decided to carry out the same procedure with a much larger number of cases, and to determine whether or not the test had any empirical value, despite the doubtful state of its theoretical basis. In doing this we have, we believe, been rewarded. The new glycerophosphate test is, on the whole, in better agreement with the clinical findings than either of the two older tests in routine use in this hospital, namely the phenolsulphonephthalein excretion and the urea concentration tests.

We propose first to describe the exact technique employed, then to point out the advantages and disadvantages of the test, and finally to give an account of the clinical and biochemical findings in the cases investigated, briefly discussing these results as they impinge on modern views with regard to renal disease.

Technique of the Test.

At about 6 a.m. the patient is given a light breakfast, devoid of fat, in order to prevent, as far as possible, a lipaemia. At 8.30 a.m. he is told to empty the bladder, and at 9.30 is given 400 c.c. of water. At 10.30 a.m. the first (2 hours) specimen of urine is collected and measured, and a portion taken for total phosphorus analysis. (At this stage a resting blood sample may be taken, if required.) 10 c.c. of glycerophosphate in approximately 50 per cent. sterile solution is then *slowly* injected into the median basilic vein from a record syringe.[4]

The time is now taken. Exactly one hour after the end of the injection, the second sample of urine is collected (taking precautions to empty the bladder completely), and measured. After precipitating the proteins with trichloroacetic acid, phosphorus determinations (free and total P) are made in duplicate on both urinary samples, using a modified Brigg's method. The 'normal' urinary excretion of phosphorus in mg. per hour is calculated from the values in the first specimen (8.30–10.30 a.m.) and it is assumed that this rate would be maintained approximately in the next hour. By subtracting the hourly 'normal' value from the amount of organic plus inorganic P in the hour following the injection, the 'excess phosphorus excretion' is obtained.[5]

Reduced to its simplest form, the test, apart from the injection, merely entails the collection of two specimens of urine, and the determination of total phosphorus in each. If the excess total phosphorus excretion in the second hour is less than 150 mg. P, then it is very probable that there is renal damage; the less extra phosphorus is excreted the greater the extent of the damage. In the terminal stages of chronic nephritis there is little, if any, extra phosphorus excreted. The assumption that the rate of excretion of phosphorus per hour from 8.30 a.m. to 11.30 a.m. is approximately constant is unlikely to introduce any serious error. Broadhurst and Leathes (6), and Fiske (7) have shown that although the hourly excretion of phosphate by the kidney is lowest in the morning, yet there are no marked variations from hour to hour during the early

[4] The dose given should contain 550 mg. phosphorus. Samples of sodium glycerophosphate vary a good deal in their water content, and an analysis should be made of each new sample so that a solution containing exactly 550 mg. of organic P per 10 c.c. can be readily made up. It is convenient to prepare a batch of ten or more ampoules (each containing 11 c.c.) from a glycerophosphate solution of the correct strength, and to seal and sterilize them together.

[5] The *relative proportion* of organic to inorganic phosphorus excreted during the test period appears to have no clear relationship with the type or the severity of the case under investigation.

part of the day. A few experiments of our own have also indicated relatively small variations at this time of the day, either in normal or nephritic subjects.

It is of interest at this point to compare analyses obtained on examining the 8.30–10.30 a.m. urine [6] of six normal cases and that of six patients with severe chronic nephritis at the same time of day. The figures are in Table I.

TABLE I

Normals.			Nephritics.		
Case No.	Mg. P excreted.		Case No.	Mg. P excreted.	
	per hour.	per 100 c.c. urine.		per hour.	per 100 c.c. urine.
45	17	11	41	22	22
95	7	7	86	23	28
96	20	17	99	25	27
97	19	7	111	11	24
114	19	8	113	26	26
115	17	12	118	45	27
Mean	16	10	Mean	25	26

The patients with chronic nephritis excrete on the whole more phosphate in this period than do the normals, and the concentration in the urine is considerably higher in the former group, and fairly constant from one individual to another. There are, of course, marked fluctuations in the rate of phosphate excretion by the normal kidney during twenty-four hours, whereas in certain cases of severe chronic nephritis the hourly rate during the twenty-four hours may change hardly at all. It is possible that the constantly high 'pressure head' of inorganic phosphate in the plasma in this disease may keep the residuum of functional kidney tissue working continuously night and day at or near its maximal activity.[7] The variations in excretory rate in normal individuals may even be of service in maintaining the health of the kidney, by allowing it periods of relative rest, during which certain of its activities are much diminished.

Advantages and Disadvantages of the New Method.

Advantages. 1. A simple, harmless 'physiological' substance is used, which is readily obtained pure, and may be handled and sterilized without decomposition. After slow injection, as just described, we have never observed any untoward results, and usually no disagreeable sensations are reported. The substance has been administered without ill effects to patients with a high plasma phosphate and marked uraemia.

2. The substance being given intravenously, there is no doubt about its having entered the circulation. With test compounds given by mouth (as in

[6] This is, of course, before any injection of sodium glycerophosphate has taken place.

[7] This is clearly associated with the well-known phenomenon of the fixation of the specific gravity of the urine, usually to be observed in such cases.

the urea concentration test) or injected intramuscularly (as in the phenolsulphonephthalein test) the quantity actually entering the circulation is a rather doubtful variable.

3. The preparations necessary to carry out the test are simple, and the requisite analyses may readily be performed in any reasonably equipped clinical laboratory.

4. There is a general consensus of opinion (8, 9, 10) which is also supported by our own findings, that the excretion of phosphate by the kidney is largely independent of the volume of urine passed, so that the glycerophosphate test is hardly affected by this variable.

5. The glycerophosphate test is unaffected by the presence of blood in the urine, or by urinary pigment.

Disadvantages. The first two disadvantages apply to all the renal function tests in common use.

1. The urinary specimens obtained may be incomplete. In the present series of tests we have exercised special care to avoid this error, and in some instances where we suspected that all the urine had not been passed, the subjects were catheterized.

2. The difficulty of adjusting the size of the dose to the individual is always present. If the dose is based on the weight of the patient there is the complicating factor in many cases, of the oedema fluid. We have therefore given the same dose of 550 mg. P to all patients. By setting the limit of extra phosphorus excretion fairly low at 150 mg., any figure below this limit indicates some degree of renal involvement, no matter what the weight of the individual. As yet we have used this test almost entirely on adults.

3. The determination of total phosphorus requires a certain amount of practice before the results can be relied upon. A method has been described by F. B. Byrom and one of us (12) for determining the total P on 0·3 c.c. blood. This method works extremely well for urine also. The amount of trichloroacetic acid filtrate to be taken for incineration depends on the urinary volume, a valuable indication of the amount to be taken being obtained by determining the *inorganic* P present in 1 c.c. of the protein-free filtrate.

An Example of the Test.

Case 34 (a case of fairly severe nephritis) may be given as a typical example of the test. It is one of a number of cases in which samples of blood as well as urinary samples were taken at intervals. Fig. 3, which shows the results graphically, may be taken as a fairly typical portrayal of the course of the changes in plasma and urinary phosphate following the administration of the standard dose of glycerophosphate to a patient with nephritis. The closely shaded rectangles represent the quantities of extra organic and inorganic phosphorus excreted in the hour's test period; it is the sum of these two quantities which is taken as the measure of renal efficiency. In this case the

extra excretion is very low, 18 mg. P only, whereas in 17 normal cases the average extra excretion in the hour following the injection is 200 mg. P. As just mentioned, 150 mg. may be taken as the lowest limit of normal 'extra phosphorus' excretion under the experimental conditions here described.

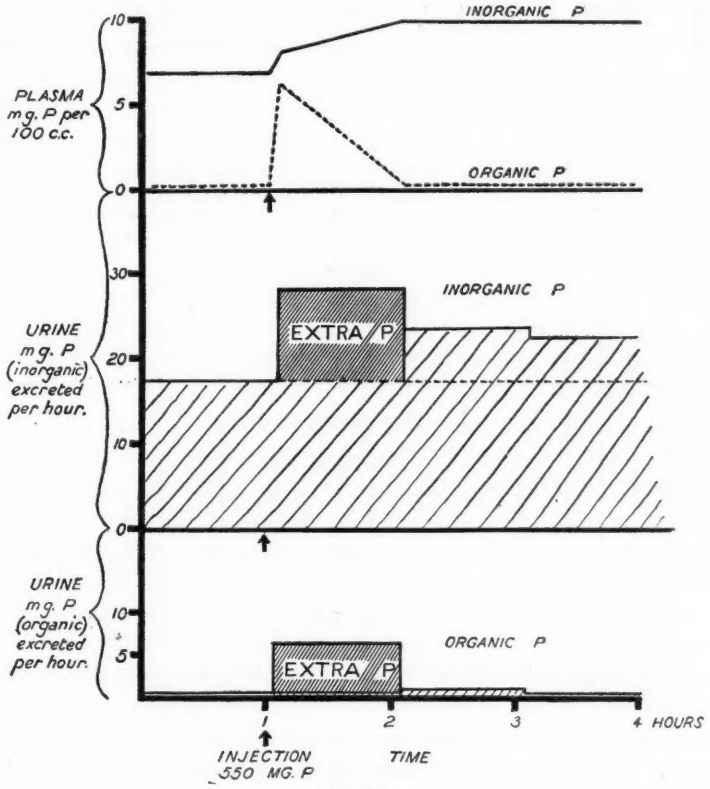


FIG. 3.

Results Described.

The total number of cases submitted so far to the glycerophosphate test is 61; 17 being normal controls and the remaining 44 being, in the main, cases of definite renal disease. A few doubtful cases, however, are here included. In the majority of the 44 cases the urea concentration test and the phenolsulphonephthalein tests[8] have also been carried out. In Fig. 4 are shown graphically a few typical examples of the results obtained with the three tests, in each of four groups of cases of renal disease. The three tests agree, it will be observed, fairly satisfactorily with one another. Clinical and laboratory findings in 40 of the cases of renal disease are given in Table II. On the whole the dye test

[8] The routine tests usually employed in this hospital.

corresponds less well with the clinical findings than either of the other two. Bowen (1) also found that the dye test was less reliable than the urea concentration test of MacLean.

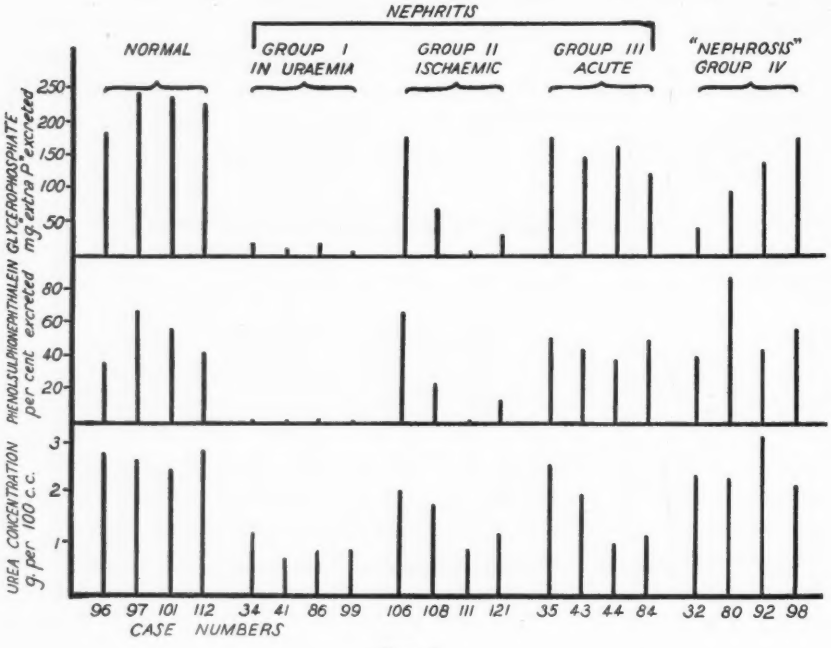


FIG. 4.

All biochemical tests of renal function, including the glycerophosphate test, are subject to certain severe limitations. Thus there is good reason to believe that one-fifth to one-sixth of the total kidney substance present in the normal individual is actually sufficient to maintain normal excretory function. As long as there is this amount of healthy kidney tissue the tests of renal efficiency may indicate little or no impairment. It is evident, therefore, that chronic destructive or degenerative changes may continue for a considerable time and may reveal on post-mortem examination a conspicuous pathological condition and yet be unaccompanied by any evidence, from laboratory tests, indicative of renal insufficiency.

Examination of kidneys from certain cases of chronic nephritis suggests that the individual kidney units are successively involved and become functionally inert, and that finally the damaged glomeruli and the essential portions of the tubules are replaced by fibrous tissue. Probably this also occurs in cardiovascular diseases and in amyloid disease, and as a result, although there is usually clear clinical evidence of the presence of a pathological condition affecting the kidney, the biochemical tests may reveal little or nothing of the state of affairs until the kidney reserve is to a large extent destroyed. Definite informa-

tion from 'renal efficiency' tests in these conditions is only to be obtained at an advanced stage, after other evidence of renal insufficiency has appeared.

Twelve cases of chronic nephritis in the terminal stage are shown in the first group in Table II. Renal failure is exhibited equally strikingly by both clinical and biochemical examination. In the majority of these cases the following characteristic features are displayed:

(i) A systolic blood-pressure of about 200 mm. Hg or over.

(ii) A definite secondary anaemia.

(iii) A blood urea concentration greater than 0·1 grm. per 100 c.c.

(iv) A low fixed specific gravity of the urine.

(v) A plasma inorganic phosphate of more than 5 mg. per 100 c.c.

(vi) Gross renal impairment as shown by renal efficiency tests, i. e. little or no excretion of phenolsulphonephthalein in two hours; a urea concentration test showing less than 1 per cent. in the second hour; and a glycerophosphate test showing less than 30 mg. extra phosphorus excretion.

One or two of the cases shown in this group present atypical features. Thus Case 86, a youth, 17 years old, was admitted to hospital in definite uraemia, but without any history suggestive of nephritis. Although the clinical picture was that of severe terminal nephritis his blood-pressure was only 130/75. There was fixation of the specific gravity of the urine, with 1/10 volume of albumin and granular casts; his blood urea rose and at one time reached 0·45 per cent. Nevertheless the disease did not, apparently, progress and he was finally discharged from hospital. He was regarded as either a case of congenital cystic kidney, or a case of 'contracted white kidney' without the usual high blood-pressure and cardiovascular hypertrophy (Rose Bradford, 11).

Case 99, a youth of 18, had also an unexpectedly low blood-pressure. In this case the tests were repeated after five weeks' interval, the results being shown as 99 A. The two groups of tests agree very well, but at the second examination a slight rise in the blood-pressure and a considerable rise in the blood urea from 0·19 per cent. to 0·31 per cent. was revealed. This patient had a three years' history of persistent albuminuria and transient oedema. Apart from the blood-pressure the clinical features revealed in hospital were those of a chronic nephritis with impending uraemia. He died in hospital from pericarditis, and unfortunately a post-mortem examination was not obtained.

In Case 30, with the exception of the glycerophosphate test, the other biochemical tests did not suggest serious renal impairment. Thus the blood urea was 0·07 per cent., 39 per cent. of phenolsulphonephthalein was excreted in 2 hours, and the urea concentration was just over 2 per cent. The plasma inorganic phosphate was, however, 4·9 mg. per 100 c.c. The urine contained 1/8 volume of albumin, with granular and hyaline casts, and the specific gravity was not fixed. The patient was a woman of 22 with a 14 weeks' history of oedema of the face and ankles. On entry into hospital she had moderate oedema, slight anaemia, and a blood-pressure of 200/120, but no retinitis. Later she became more oedematous and developed uraemic fits. Retinitis was

observed during a short remission. The patient died in uraemia six weeks after this remission. It should be pointed out that in this particular case the glycerophosphate test contradicted the other renal function tests and proved to be right in indicating a severe degree of renal impairment.

In the second group of Table II are four cases of primary arterial hypertension with secondary ischaemic nephritis (13). The recognition of these rather infrequent cases as distinct from those of true chronic nephritis is a matter of some difficulty, and for this reason typical cases only are recorded in this group.

The peculiar features which we regard as distinctive in these four cases are as follows:

Case 106 had a high blood-pressure and marked cardiovascular hypertrophy with some haemorrhages and exudate in the retina. Nevertheless, the evidences of renal insufficiency were slight and the tests of renal efficiency were normal.

Case 108 was admitted to hospital with heart failure and marked cardiovascular hypertrophy and gave a history of having had a stroke twelve years previously. The renal condition was clearly of secondary incidence. The patient died of heart failure. Post-mortem a red granular kidney was found, confirming the diagnosis.

Case 111 was known to have had a high blood-pressure and no albumin in the urine on six examinations during the seventeen years preceding her admission to hospital. She died at home apparently in uraemia.

Case 121 was admitted with heart failure of which he died. Post-mortem examination showed 'red granular kidney' and the histological appearances characteristic of advanced ischaemic nephritis.

It is noteworthy that in the last two cases there is not the marked secondary anaemia which is so characteristic of the advanced stage of chronic nephritis. Professor Arthur Ellis informs us that it is very unusual in his experience for ischaemic nephritis following primary arterial hypertension to progress to the degree seen in cases 111 and 121. Usually death from cerebral haemorrhage or from cardiac failure supervenes before the degeneration of the kidney has reached the stage at which gross impairment of function is manifest. These two cases are the most severe examples of ischaemic nephritis he has seen.

The evidences of renal insufficiency illustrated by the foregoing groups of patients are probably the result of a progressive destruction of excretory units, which finally leads to the exhaustion of the relatively large physiological reserve of the organ. In some cases, however, there is little doubt that the whole kidney suddenly fails. Severe toxaemias and acute infections may be accompanied by partial or even complete suspension of kidney function. In these cases the impairment of function during the acute stage is in no sense indicative of the extent of permanent renal damage. Even where total anuria has supervened at some stage, there may yet be an apparently complete recovery. In this group of cases, where the renal impairment is a fluctuating and reversible

process, the results of renal function tests will naturally fluctuate from time to time according to the condition of the organs. Group III in Table II and the corresponding group in Fig. 4 show examples of this type of case, namely of acute nephritis. The essential features of these cases may be regarded as (*a*) a short history, (*b*) the presence of blood in the urine. Almost any combination of findings or symptoms associated with chronic nephritis may be present also. In most of the cases the blood-pressure was moderately raised, and there was a slight increase in blood urea and in plasma inorganic phosphate.

In Group IV of Table II are the results of the investigation of four cases which present most of the features ascribed to cases of so-called 'nephrosis'. The characteristics of such cases are:

(i) A marked oedema.
(ii) A large amount of albumin in the urine.
(iii) An approximately normal blood-pressure.
(iv) A normal blood urea.
(v) No marked disturbance of the usual tests of renal function.

There is usually an increase in the blood cholesterol and a decrease in the plasma proteins, especially in the serum albumin, with a corresponding decrease in the osmotic pressure of the plasma colloids.

The glycerophosphate test showed some deviation from the normal in four of these six[9] examinations, the phenolsulphonephthalein test in three out of the six and the urea concentration test was normal in all. There is some indication that the glycerophosphate test is, if anything, more sensitive in this group of cases than the other two tests employed.

The more critically one surveys the cases in this group, the more difficult it becomes completely to justify their classification as cases of 'nephrosis', implying thereby renal degeneration as distinct from inflammation. Thus in two of the four cases (nos. 36 and 98) although clinically there was no haematuria, yet along with granular and hyaline casts *some red cells* were present in the urine at the onset. This might be taken as indicative of acute nephritis. Moreover, Case 36 gave a previous history of scarlet fever, whilst Case 98 had had a sudden onset like that of acute nephritis. In the latter case the marked oedema persisted, and renal function tests gave normal results on three occasions during the two months preceding the date of the tests here reported. It would appear that this case might equally well be classified as one of chronic nephritis.

Other cases of chronic nephritis are shown in Group V of Table II. In most of these only slight degrees of renal incompetence were found, and it is not easy to assess the true value of the biochemical tests. (The results of the dye test in Cases 91 and 96 are probably erroneous.)

Case 100 presented the usual features of primary arterial hypertension with secondary ischaemic nephritis, but the condition was regarded as being a toxaemia of pregnancy. This would appear to have been correct, for when

[9] 36 A is a repeat test on Case 36 after an interval of four months; 92 A a repeat test on Case 92 after an interval of five weeks.

examined four months later the patient was free from symptoms and only a slight cloud of albumin was found in the urine.

We are aware that the number of cases reported by us is at present too small to form the basis of any serious contribution to the clinical study of nephritis. We are publishing our findings at this stage mainly because our experience of the glycerophosphate test has been decidedly favourable, and has led us to hope that this test may be found by others to be of real service in the clinical assessment of the degree of renal involvement in various types of Bright's disease.

Summary.

1. A new test of renal efficiency, the 'glycerophosphate test' is described. It depends upon the excretion of extra phosphorus in the urine in the hour following the intravenous injection of a standard quantity of organic phosphorus (550 mg.) in the form of sodium glycerophosphate. In normal individuals, or in patients not suffering from renal disease, at least 150 mg. extra phosphorus is excreted in this period; in cases of renal impairment the amount varies from this figure down to 0 mg. depending on the severity of the renal damage.

2. The test is simple to carry out, and is not subject to certain errors associated with the urea concentration and phenolsulphonephthalein tests.

3. Comparisons have been made, in forty-four cases of renal disease, between this test and the urea concentration and phenolsulphonephthalein tests. The information provided by the glycerophosphate test has been everywhere at least as valuable as that derived from the other two tests, and in certain instances where there has been a divergence between them, the glycerophosphate test has agreed most closely with the clinical findings.

The authors wish to record their grateful appreciation of the advice and assistance given them by Professor Arthur Ellis. They are indebted to the Trustees of the Research Fund of the London Hospital Medical College for a grant towards the expenses of the work. One of the authors (H. D. Kay) is working under the tenure of a Beit Memorial Fellowship.

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TABLE II.

Case No.	Age.	Sex.	Anaemia.	Oedema.	Retinitis.	Blood-pressure.	Blood Urea. %	Plasma Inorganic Phosphorus. %	Albuminuria.	Casts in Urine.	Sp. Gr. of Urine Fixed.	Urea Concentration Test. %	Phenol Sulphone Phthalein Test.	Glycerophosphate Test.
Group I. *Chronic Nephritis. Terminal Stage.*														
29	43	M.	Mod.	Slight	Mod.	200/120	0·3	8·4	1/6 vol.	No	Yes	—	—	50
30	22	F.	Slight	Mod.	None	200/120	0·07	4·9	1/8 vol.	Yes	No	2·0	39	22
34	20	F.	Severe	Slight	Mod.	130/70	0·18	6·9	Trace	No	Yes	1·2	—	18
39	36	M.	Mod.	None	Severe	240/140	0·13	5·2	1/3 vol.	No	Yes	0·9	Trace	31
41	26	M.	Severe	Slight	None	185/125	0·3	9·8	1/3 vol.	Yes	Yes	0·7	None	10
86	17	M.	Mod.	Slight	None	130/75	0·29	11·6	1/10 vol.	Yes	No	0·9	Trace	18
99	18	M.	Severe	Slight	None	130/95	0·19	9·6	1/12 vol.	Yes	Yes	0·9	Trace	4
99*a*	18	M.	Severe	Slight	None	142/98	0·31	9·6	1/2 vol.	Yes	Yes	0·9	Trace	11
104	47	M.	Mod.	Slight	None	155/98	0·18	—	1/6 vol.	Yes	Yes	1·2	11	13
105	33	M.	Mod.	Slight	Severe	220/135	0·17	5·8	1/6 vol.	Yes	No	0·7	27	24
118	40	M.	Mod.	Mod.	Slight	235/130	0·21	7·8	7/8 vol.	Yes	No	0·9	None	0
119	26	M.	Severe	Slight	Slight	200/150	0·19	7·5	1/3 vol.	No	Yes	1·0	Trace	13
Group II. *Secondary Ischaemic Nephritis.*														
106	52	M.	None	None	Slight	205/140	0·05	3·4	1/6 vol.	No	No	2·0	66	178
108	44	M.	None	Slight	Mod.	240/160	0·07	—	1/3 vol.	Yes	No	1·8	24	69
111	51	F.	Slight	None	Severe	260/150	0·1	6·8	1/3 vol.	Yes	Yes	0·9	Trace	3
121	38	M.	Slight	Mod.	Severe	220/160	0·07	3·9	1/2 vol.	No	No	1·2	14	32
Group III. *Acute Nephritis.*														
35	16	M.	None	None	None	125/80	0·05	3·6	1/20 vol.	No	No	2·6	52	180
43	20	M.	None	Slight	None	162/95	0·05	4·5	1/16 vol.	No	No	2·0	45	150
44	24	M.	Slight	Slight	None	165/92	0·05	4·0	1/6 vol.	Yes	No	1·0	39	167
82	18	M.	Slight	None	None	142/85	0·03	4·2	1/16 vol.	Yes	No	1·6	72	166
84	17	M.	Slight	None	None	144/75	0·03	5·2	1/5 vol.	Yes	No	1·2	51	124
87	33	M.	None	None	None	190/90	0·06	4·0	1/6 vol.	Yes	No	1·3	47	147
94	22	M.	Slight	Slight	None	170/105	0·03	3·5	1/12 vol.	Yes	No	1·7	51	197
98	14	F.	None	Marked	None	105/60	0·04	4·5	3/4 vol.	Yes	No	2·2	56	174
109	19	M.	None	Mod.	None	135/85	0·04	3·2	1/6 vol.	Yes	No	1·5	—	116
120	13	F.	None	Slight	None	124/80	0·04	4·6	1/3 vol.	Yes	No	2·0	66	187

TABLE II (*continued*).

Case No.	Age.	Sex.	Anaemia.	Oedema.	Retinitis.	Blood-pressure.	Blood Urea. %	Plasma Inorganic Phosphorus. %	Albuminuria.	Casts in Urine.	Sp. Gr. of Urine Fixed.	Urea Concentration Test. %	Phenol Sulphone Phthalein Test.	Glycerophosphate Test.
Group IV.	*'Nephrosis.'*													
32	34	M.	Slight	Marked	None	145/95	0·04	3·0	7/8 vol.	No	No	2·4	40	41
36	18	M.	Slight	Marked	None	135/80	0·05	6·5	1/3 vol.	Yes	No	2·0	58	96
36*a*	18	M.	Slight	Mod.	None	142/80	0·04	6·7	1/3 vol.	Yes	No	2·3	87	97
92	23	M.	None	Mod.	None	135/100	0·04	3·3	7/8 vol.	No	No	3·0	45	141
92*a*	23	M.	None	Mod.	None	130/90	0·03	—	1/3 vol.	No	No	2·1	39	158
98	14	F.	None	Marked	None	105/60	0·04	4·5	3/4 vol.	Yes	No	2·2	56	174
Group V.	*Chronic Nephritis, Unclassified.*													
33	16	M.	None	Mod.	None	130/110	0·02	4·1	1/2 vol.	Yes	No	2·1	76	160
37	48	M.	None	None	None	130/84	0·07	4·0	Cloud	No	No	1·8	43	80
83	20	F.	Mod.	None	Slight	170/105	0·05	4·5	1/3 vol.	Yes	No	1·5	63	120
85	19	M.	None	Slight	None	176/95	0·07	4·2	1/2 vol.	No	No	0·9	—	54
91*	25	F.	None	None	None	120/90	0·03	3·4	Trace	No	No	2·6	16	227
96	55	M.	None	None	None	170/100	0·04	3·4	Cloud	No	No	2·8	37	179
100*	30	F.	None	Mod.	Mod.	220/140	0·08	4·0	1/2 vol.	Yes	No	1·4	32	82
122	50	M.	Mod.	Mod.	None	180/105	0·06	3·8	1/10 vol.	Yes	No	1·1	36	68

* Onset during pregnancy.

AN AETIOLOGICAL STUDY OF PRIMARY GRAVES' DISEASE[1]

WITH SPECIAL REFERENCE TO THE SIGNIFICANCE OF THE SEX EVENTS OF THE FEMALE

By H. GARDINER HILL

(From the Medical Unit, St. Thomas's Hospital)

The main object in view in the present investigation has been to estimate the significance of the various events of the female sex life—puberty, menstruation, pregnancy, the puerperium, and climacteric—as factors in the aetiology of primary Graves' disease. In order, however, to present this side of the problem in its proper perspective, observations have been made on a complete series of cases, male and female. It is strange that, although the literature of the aetiology of this disease is so extensive, and numerous references are made to the importance of these events, up to the present the subject has only been considered in a general way. And yet it has frequently been pointed out that the incidence of Graves' disease is more or less limited to the period of active sex life. There is, however, no definite information available as to the proportion of cases occurring at the time of the sex events relatively to those at other times, nor has any critical investigation been undertaken as to the relationship between these events and the onset of symptoms. Further, nothing has been worked out as to their interrelationship with the other factors, notably, mental anxiety, worry, sudden shock, and infections, which so frequently precipitate the disease.

The present state of our knowledge of the aetiology of this disease has recently been summarized by Fraser (1). He says: 'We are quite ignorant of the cause of primary Graves' disease, or of the exacerbations and relapses which are its common features. Adolescence, pregnancy, the puerperium, and the menopause appear to be dangerous events. Infections, and above all septic tonsils, nasal sinuses, and teeth defects, are particularly important because so often overlooked. Worries, mental stresses, and shocks are also important, and are often acknowledged by the patients, but are sometimes not disclosed unless skilfully inquired for.'

Eason (2) in a recent text-book has expressed similar views, though he points out that what is unknown is pathogenic rather than aetiologic; for, as he says, the circumstances under which Graves' disease develops are known with remarkable definiteness in the majority of cases. The influence of heredity is

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important. The influence of environment, especially in childhood, adolescence, and early adult life, is important. Mental and physical strain and infections are the most common exciting factors. A combination of these is probably the most effective cause of the disease. To account for the high incidence in the female sex, especially during the period of active sex life, he suggests that the greater ebb and flow of activity in the endocrine glands and nervous system during puberty, menstruation, pregnancy, childbirth, the puerperium, and the climacteric is probably largely responsible.

These views of Fraser and Eason are no doubt representative of present-day opinion. The results of the present investigation will be found to support them fully.

Historical.

The importance of psychic trauma in the aetiology of Graves' disease has been emphasized by many writers, and full reference will be found in the works of Murray (3), Mackenzie (4), and McCarrison (5). Thompson (6) has called attention to the importance of infections as exciting factors, and he considered that they were responsible for the onset of the disease in 25 per cent. of his 80 patients. Swan (7) gives similar figures in a series of 50 cases in which acute infections gave rise to symptoms in 13. There is little precise information, however, as to the influence of the incidents of the female sex life. Two recent surveys are of interest. Watson (8) (1917), in an investigation into the causes of exophthalmic goitre, gave the following percentage figures: worry, 15 per cent.; parturition, 11 per cent.; puberty, 9·6 per cent.; influenza, 4 per cent.; pregnancy, 3 per cent.; climacteric, 3 per cent.; in others fright, grief, typhoid fever, diphtheria, scarlet fever, injury to thyroid, iodine or potassium iodide administration, and operation shock. In this series, therefore, the incidents of the female sex life played an important part in the onset of 26·6 per cent. of cases. Bram (9) (1927), in his series of 3,343 cases seen during a period of 15 years, gives the following figures: *Group I, psychic trauma*—(*a*) accident or imminent personal danger, 13 per cent.; (*b*) minor surgery, tonsillectomy, &c., 7 per cent.; (*c*) parturition, 4 per cent.; (*d*) worry, grief, disappointment, 61 per cent. *Group II, infections*—(*a*) general infections (influenza, pneumonia), 3 per cent.; (*b*) focal infections, i. e. teeth, tonsils, &c., 2 per cent. *Group III*—(*a*) iodine ingestion, 3 per cent.; (*b*) thyroid extract ingestion, 1 per cent. *Group IV*—no stated cause, 6 per cent.

Apart from these series of cases there is a general tendency in the literature to regard puberty and the climacteric as dangerous events, though with regard to the climacteric, as Garnier and Huguenin (10) point out, even if Graves' disease does develop sometimes after this event, either natural or artificially induced, it is far from being the rule in castrates.

There is considerable disagreement as to the role of pregnancy as an aetiological factor. Crotti (11) (1922), for instance, says that it is a well-known fact that Graves' disease may develop either during or at least in connexion

with pregnancy; but in his quotations from the literature he brings forward no evidence in support of this statement. McCarrison (5), in his book on the thyroid gland, does not mention pregnancy as an aetiological factor in Graves' disease. Dock (12) (1927) states that sometimes Graves' disease begins in pregnancy or in the puerperal period, and Howard (13) (1922) also observes that pregnancy and lactation play an important but by no means a consistent role in the aetiology of this disease. As has already been stated, Eason (2) (1927) is of the opinion that it is probably a factor of importance, though he does not consider that up to the present the influence of the various incidents of married life as factors in the development of the disease has been satisfactorily worked out. He states, however, that under unfavourable circumstances, psychic and toxic, Graves' disease may develop during pregnancy and the puerperium. Recently an important investigation as to the association of pregnancy and Graves' disease has been carried out by Murray, Plummer, and Boothby (14) (1926), but it is chiefly from the aspect of pregnancy as an event in this disease rather than from that of its influence as an aetiological factor. In a series of 5,043 cases of exophthalmic goitre these authors found that only 32 were pregnant. They state that in only 2 of the 32 cases could the onset of the disease be considered with reasonable certainty to have developed during pregnancy, but they do not say in what proportion of the remainder of the whole series pregnancy may have played some part as an aetiological factor.

Terminology.

Of recent years there has been a tendency to differentiate several varieties of the Graves' syndrome, the classifications being made chiefly on a histopathological basis. Plummer (15), for instance, described two types of the disease, true exophthalmic goitre presenting the classical picture of Graves' disease, and toxic adenoma, a slowly progressive condition in which symptoms of intoxication appeared after some years in an existing goitre, the latter being harder, more irregular, and less vascular than in the typical form. In the latter cases, also, the eye signs were usually less prominent and the cardiac disturbance relatively more marked than in true Graves' disease. Williamson and Pearse (16) have also made extensive observations, classifying their cases on a pathological basis. They recognize true primary Graves' disease and secondary Graves' disease. In the former the classical picture of Graves' disease is presented and the thyroid changes are those of an 'adenoid goitre' in 100 per cent. of cases. The secondary type, on the other hand, may be associated with the fine fibrotic goitre (arteriocapillary sclerotic goitre) or the coarse (adenoparenchymatous or toxic adenoma), these being the results respectively of secondary fine or coarse fibrosis in a simple hypertrophic goitre. Williamson and Pearse also recognize a primary arteriocapillary sclerosis of the gland, usually part of a general arteriocapillary fibrosis, which may be associated with thyrotoxic symptoms. In 65 per cent. of these cases they say that the symptoms are those of hyper-

thyroidism without exophthalmos, variously termed toxic goitre, or 'formes frustes' by clinicians, whilst in 25 per cent. the symptom-complex of Graves' disease develops.

In the present investigation it has only been possible to classify the cases on clinical grounds, and the terms primary and secondary have been employed in their broadest sense to indicate respectively cases in which symptoms of intoxication were present from the start, and others in which intoxication developed later in an existing goitre. Those of the former type only, primary Graves' disease, have been included in the statistics in the present paper.

The majority of these cases, and especially those which occurred in adolescence and early adult life, presented the classical picture of primary Graves' disease with diffusely enlarged and vascular goitres, eye signs, tremor, tachycardia, and nervousness. This picture was also seen in a number of the older patients, but in others the gland was less enlarged, less vascular, harder, and more irregular than in the typical form, though symptoms of intoxication had been present from the onset. In these patients the eye signs were usually less prominent, though the cardiac disturbance was relatively more marked. Many of them developed symptoms of the disease about the time of the climacteric, but there were very few instances in earlier life. This group probably includes cases such as those described by Williamson and Pearse under the heading of primary arteriocapillary sclerosis, the 'formes frustes', incomplete forms, toxic goitre, and thyrotoxicosis of other observers.

The Present Investigation.

The present investigation has been carried out at St. Thomas's Hospital between the years 1921 and 1928. During this period the author has been given facilities by the members of the staff of the hospital for examining a large series of cases of thyroid disease and investigating the circumstances which led to the onset of symptoms. The important influence of the events of the female sex life in the aetiology of many of the cases of Graves' disease has been apparent from the outset and records have consequently been kept in all cases of the course of such events as puberty, menstruation, pregnancy, the puerperium, and climacteric. The data of the present investigation are based on these records. Two hundred and six cases of primary Graves' disease have been examined. They have not been selected in any way and represent all cases seen by the author in which it was possible to obtain adequate information.

For purposes of subsequent discussion, these 206 cases have been divided into sex and age groups as follows:—(1) Adolescent females: onset before the age of 20. (2) Single women: onset between the age of 20 and the climacteric. (3) Single women: onset at the climacteric or after. (4) Married women: onset between the age of 20 and the climacteric, during pregnancy, the puerperium, or after miscarriage. (5) Married women: onset between the age of 20 and the

climacteric at times other than above. (6) Married women: onset at the climacteric or after. (7) Males, adolescent and adult.

Classification, Age and Sex Incidence.

In Table I will be found a classification based on the above age and sex grouping.

TABLE I. *Classification of 206 Cases.*

Females 183. Males 23.

	Female.	Male.
1. Adolescent:		
Up to 20	32	6
2. Adult:		
(*a*) Single	59 *x**	4
(*b*) Married	71 *y*†	13
(1) Pregnancy and puerperium	29	—
(2) Others	42	—
3. Menopause or after:		
(*a*) Single	4	—
(*b*) Married	17	—

* *x* includes 12 cases with eye signs absent or slight.
† *y* includes 9 cases with eye signs absent or slight.

It will be seen that the incidence in women is much higher than it is in men; in my patients a proportion of 183 women to 23 men or, roughly, 8 : 1. This corresponds fairly closely to the figures given by other observers.

There is little comment to be made on the male cases except to mention that of the 17 adults 13 were married. All the 23 male cases occurred during the period of active sex life.

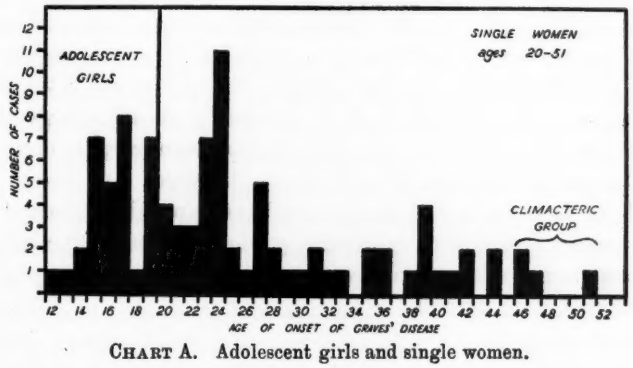


CHART A. Adolescent girls and single women.

The age incidence of the female cases can best be studied in Charts A and B, in which the number of cases occurring at any given age is given. It will be seen that the occurrence of Graves' disease is largely limited to the period of life between puberty and the climacteric.

The incidence in girls and single women (Chart A) is highest up to the age of 25, after which there are comparatively few cases at any given age. Graves' disease in girls starts abruptly at puberty, a relationship which will be studied more fully in a subsequent section, and continues at a high level throughout adolescence. This high incidence is also maintained in single women in early adult life, and it is to be noted that 61 per cent. of the cases in single women occurred in the first seven years of adult life. These figures correspond to those of Eason, who in a series of 75 cases found that in 13 the disease began before or during the twentieth year, in 23 between the ages of 21–25, in 15 from 26–30, in 7 from 31–35, and in 9 from 36–40. The incidence was, therefore, highest in the five-year period 21–25. In his series, single and married women were included together. In the present series, they have been considered separately. The incidence in married women is shown in Chart B.

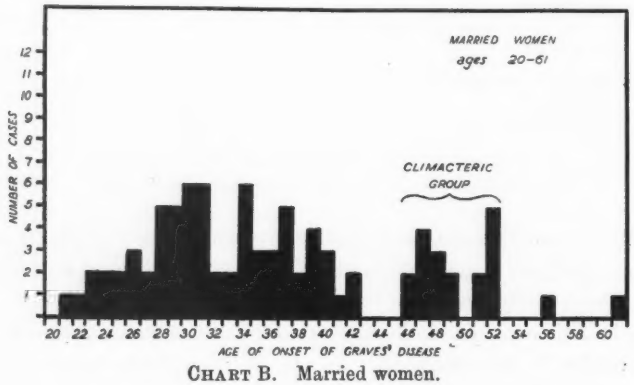


CHART B. Married women.

It will be seen that Graves' disease in married women is considerably more frequent in middle and later life than in single women, and most cases occur during two age periods—(1) between 25 and 42 and (2) in the neighbourhood of the climacteric, 46–52. In the first group, as will be shown later, the events of pregnancy and the puerperium have apparently played a large part in the high incidence of cases, for 41 per cent. of those occurring in married women between the ages of 20 and the climacteric developed the disease in direct relationship to these events. The high incidence in married women at the time of the climacteric is also striking, especially when considered in relation to that during the same age period in single women, for of the whole group of climacteric cases 81 per cent. were married.

Extrinsic exciting Factors.

Extrinsic exciting factors, shock, mental strain, and infections, have played a prominent part in the onset of the disease in a large percentage of my cases. This is entirely in agreement with the conclusions of other observers. In order

to avoid repetition in discussing the findings in the various sex and age groups, it has been found expedient to summarize these observations in Table II.

TABLE II. *Extrinsic exciting Factors: Summary.*

	Psychic Trauma, Shock, Loss of Relative, Accident, War, Anxiety over Profession, &c.	Infections, Influenza, Tonsillitis, Abscesses, Teeth, &c.	Psychic Trauma and Infections combined.	No stated cause.
	%	%	%	%
Adolescent girls	32	28	15	25
Adolescent boys	100	—	—	—
Single women, 20 to climacteric	41	18·6	18·6	21·8
Single women, climacteric and after	—	25	—	75 (climac.)
Married women, 20 to climacteric. Preg. group	62·1	10·5	6·8	20·6
Married women, 20 to climacteric. Others	42·8	14·3	12	26·1
Married women, climacteric and after	35·3	17·6	11·8	35·3 (climac.)
Adult males	29·4	41·2	17·6	11·8

It will be seen that, if these figures are averaged out, psychic trauma alone was a precipitating factor in about 50 per cent. of cases, whilst infections alone were responsible for about 20 per cent. In an additional 10 per cent. these factors were present together.

The percentage figures for the incidence of infections correspond fairly closely to those already quoted, namely, Thompson (25 per cent.) and Swan (26 per cent.), but in the present series the incidence of psychic trauma is apparently considerably less than in the series of Bram (85 per cent.). Against this, however, is the relatively high proportion of the present cases in which no adequate extrinsic exciting factor could be elicited in the history to account for the onset of the disease. This latter figure averages out at about 20 per cent. as against Bram's 6 per cent. and is fairly constant through the various groups if those of the climacteric are excluded. The high figures, 75 per cent. and 35·3 per cent., in these latter groups appear in some measure to be explained by the number of cases which occurred as a result of the intrinsic changes of the climacteric itself. It is obvious that psychological factors in these cases cannot entirely be discounted, but they were not acknowledged by the patient and the above grouping has, therefore, been adopted.

A more detailed analysis of the individual factors under these headings shows that in adolescence psychic trauma took the form of shock or fright from accident, air raids, quarrels with parents or friends, anxiety over business or employment recently embarked upon, especially teaching, nursing, or domestic service. Similar circumstances account for a large number of the cases in single women, though in this group there is also a frequent history of shock from the

death of a relative or fiancé. In the married cases one finds such incidents cited as the shock of a motor accident, the death of a relative, the anxiety and difficulties of a confinement, or the subsequent illness or death of the baby. In the males there are many instances of the disease following grief at the loss of wife, relative, or child. In others it was the result of anxiety from experiences during the Great War.

Of toxic factors, tonsillitis and influenza were by far the most frequent cause of the disease. The incidence of tonsillitis as an exciting factor was especially high in adolescence. In single women half the cases resulting from toxic factors were caused by acute infections (influenza, tonsillitis, and diphtheria) and half by chronic septic processes, generally in the throat, nose, or ear. This is approximately true also of the series of cases in married women, though it is to be observed that fewer married women acquired the disease as a result of infections than girls or single women. In adult males, on the other hand, the influence of infection as an aetiological factor is greatest, and it should be mentioned that in all but two of the 41·2 per cent. of cases under this heading the disease followed an attack of influenza.

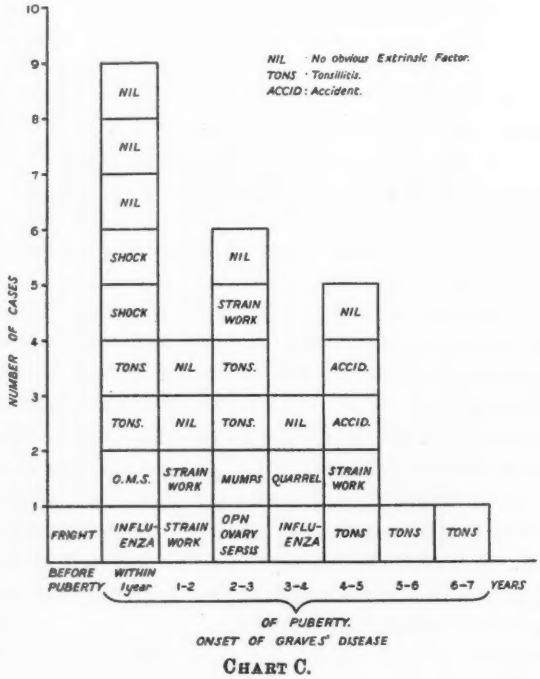


CHART C.

Relationship of Puberty to onset of Graves' Disease.

Let us now consider the relationship of puberty, the onset of menstruation, to the incidence of Graves' disease. It has already been mentioned that in the

present series of female cases, not only was the incidence practically limited to the period of active sex life, but in point of fact only one case occurred before puberty. This was in a young girl of seven, who happened to be in Germany at the outbreak of war, and in whom symptoms of the disease developed shortly after this experience.

The abruptness with which the incidence of cases develops at puberty is well illustrated in Chart C, which is based on information obtained from 30 of the 32 adolescent female cases. In this chart details of the extrinsic factors leading to the onset of symptoms are also given. In 9 cases the disease developed within one year of the onset of menstruation at puberty, the highest incidence in the series, after which there is a steplike decrease. In the remaining cases the interval between the two events was over one year in 4 cases, over two years in 6 cases, over three years in 3 cases, over four years in 5 cases, over five years in 1 case, and over six years in 1 case. The year of puberty, therefore, and those immediately following are times at which Graves' disease is especially liable to occur. Whilst recognizing that the majority of these cases are precipitated by shock, mental strain, and infections, factors to which these children are probably exposed in greater degree at this time, it is difficult not to regard the neuro-glandular changes associated with puberty as important predisposing factors.

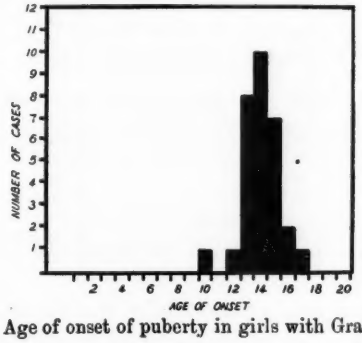


CHART D. Age of onset of puberty in girls with Graves' disease.

It has been suggested from time to time that genital disturbances, notably ovarian insufficiency with amenorrhoea, are factors of importance in the genesis of Graves' disease. Delestre (18) (1920), for instance, states that they occurred in 96 per cent. of his cases of exophthalmic goitre and usually preceded the other evidences of the syndrome, and were not, therefore, the result of the disease. There is very little evidence in support of this statement in the present series of adolescent cases. Puberty, for instance, as will be seen in Chart D, occurred within the normal age limits in the majority, in fact in practically all these girls between the ages of 13 and 15.

In the majority of cases, too, menstruation, before the onset of Graves' disease, became satisfactorily established and pursued an entirely normal course. The menstrual details of these adolescent cases are given fully in Table III.

TABLE III.

No.	Name.	Menstruation before Onset of Ex. Goitre.	Menstruation after Onset of Ex. Goitre.
1	I. J.	Two normal periods before Ex. G.	Amenorrhoea since Ex. G.
2	C. B.	N. and R.	Amenorrhoea after 2/12 Ex. G.
3	D. R.	N. and R.	N. and R.
4	F. A.	N. and R. 4/28	Amenorrhoea after 3/12 Ex. G.
5	M. J.	N. and R.	Amenorrhoea after 1/12 Ex. G.
6	A. B.	Periods of amenorrhoea 4/12 to 12/12 always	Amenorrhoea
7	M. B.	One period only puberty	—
8	L. B.	N. and R. 3/28	Amenorrhoea. P. once in 3/12
9	N. S.	N. and R. 4/28	N. and R. 4/28
10	L. H.	?	Amenorrhoea. P. every 2/12
11	L. E.	Amenorrhoea from start. Pub. 5/12 before Ex. G.	Amenorrhoea. P. every 2/12
12	M. S.	N. and R. 6/28	N. and R. 5/28
13	M. W.	N. and R. two regular periods, then Ex. G.	Amenorrhoea
14	P. P.	N. and R. twice	Amenorrhoea
15	E. M.	N. and R. 2/28	N. and R. 2/28
16	F. E.	Amenorrhoea first 2 yrs. Then N. and R.	Amenorrhoea
17	L. I.	?	?
18	M. P.	Amenorrhoea every 2/12 from start	Amenorrhoea every 2/12
19	E. L.	Amenorrhoea always every 3/12	Amenorrhoea every 3/12
20	H. B.	Amenorrhoea always every 3/12	Amenorrhoea 3/12. N. and R. since opn. hemithyroidectomy
21	M. L.	N. and R.	Amenorrhoea after 3/12 Ex. G.
22	D. B.	N. and R.	N. and R. 3 yrs. after Ex. G. now DISc.
23	E. M.	N. and R. 4/28	N. and R. 4/28
24	E. H.	N. and R. till 16½. Amenorrhoea 2/12 till 18	Amenorrhoea every 2/12
25	M. W.	N. and R. till 15. Amenorrhoea till 15½	Amenorrhoea 6/12 since Ex. G.
26	M. B.	N. and R. 4/28	DISc. 1/28
27	W. S.	N. and R. 4/28	N. and R. 4/28.
28	M. H.	N. and R. 4/28	DISc.
29	M. S.	N. and R. 4/28	N. and R. 4/28
30	M. Y.	?	?
31	M. D.	N. and R. 7/28	N. and R. for 9/12, then amenorrhoea
32	M. G.	N. and R. 3/28	N. and R. 3/28

If these observations are summarized it will be found that in 79 per cent. menstruation before the onset of Graves' disease was normal and regular. On the other hand, in 21 per cent. it had not become properly established and there was a tendency to longer or shorter intervals of amenorrhoea.

It is not, of course, possible to draw very definite conclusions from these figures, but it is obvious that menstrual disturbances did not play any part in the aetiology of the majority of cases. It may, however, have been a factor in 21 per cent., though it is probable that minor menstrual disturbances of this sort would be found in the same proportion of a series of comparatively healthy girls.

It is unwise perhaps to form any conclusions on individual cases, but the circumstances associated with the onset of the disease in the following patient are unusual and might be advanced in support of Delestre's views.

E. L. and M. L., twin sisters aged 17, had lived and been brought up under identical conditions. Until the age of 15½ they had resembled each other closely;

both were obese and equally developed. Their respective weights were 11 st. 6 lbs. and 11 st. The onset of menstruation occurred in both at the age of 13. In one (M. L.) it had always been normal and regular and of a 6/28 day type, but in the other (E. L.) it had always been irregular. This latter twin at the age of 15½ had an acute abdominal operation and an impacted cystic ovary was removed. After operation, menstruation was still irregular. Nine months after operation she developed an acute staphylococcal infection in her nose which did not clear up for two months. It was then noticed that she was rapidly losing weight. Eighteen months after operation she had lost 3 stone in weight and presented the typical picture of Graves' disease, with a vascular goitre, exophthalmos, tachycardia, and amenorrhoea. At this date her weight was 7 st. 11 lbs. as against her sister's 11 st. 5 lbs. Examination of the basal metabolic rate showed it to be +27·5 per cent., as against −11·5 per cent. in the healthy sister (M. L.), who was examined as a control.

In this case it looks as though the genital disturbance may have been an important factor in the subsequent development of Graves' disease, for, apart from the preceding history of menstrual disturbance and operation, the conditions and circumstances of the twins before the onset of the disease were, as far as could be ascertained, identical. But the alternative view could of course be upheld—that the condition might have developed in any case as a result of infection, if the ovaries had remained intact and no menstrual disturbance been present. In fact, this is probably more in keeping with the observations on the other cases of the series.

On the whole, it seems most unlikely that menstrual disturbances play any important part in the aetiology of the majority of cases of adolescent Graves' disease.

On the other hand, the observation that amenorrhoea is frequently a symptom of Graves' disease is strongly supported by the present findings. If a summary is made from Table III, it will be found that amenorrhoea of greater or lesser degree was present in 72 per cent. of these cases after the onset of the disease. In the remainder, 28 per cent., the normal rhythm of menstruation was preserved. There can be little doubt, therefore, that the suppression of menstruation was a result of the disease and not an aetiological factor. This has been the view taken by the author in a paper written recently in conjunction with Forest Smith (19), in which the menstrual irregularities in a large range of cases of thyroid disease were discussed.

Relationship of the Events of Pregnancy and the Puerperium to the onset of Graves' Disease.

The importance of the events of pregnancy and the puerperium as aetiological factors in this disease will be seen from a study of the 71 cases which occurred in married women during the child-bearing period, that is, prior to the climacteric. In this series, 62 of the patients presented the typical picture of primary Graves'

disease with well-marked eye signs, whilst in 9 the eye signs were absent or slight. The highest incidence of cases, as has already been mentioned, occurred between the ages of 25 and 42.

In 29 of these patients, that is 41 per cent., symptoms of Graves' disease first developed in relation to the events of pregnancy (8 cases), the puerperium (16 cases), or after miscarriage (5 cases). In these cases, as in the majority of others, the determining factor in the onset of the disease would appear to have been either shock, mental stress, or sepsis. This side of the problem has already been discussed. In the 5 cases in which symptoms first appeared after miscarriage it is most probable that the mental trauma which caused the miscarriage (there was a history of this in 4 cases) was also the major factor in the onset of the disease, though no doubt disappointment at the turn of events had an important influence subsequently. The actual incidents which precipitated the disease in these 5 cases were as follows: Case 1, shock of air raids; Case 2, anxiety at husband's attitude to pregnancy; Case 3, shock of operation resulting from miscarriage; Case 4, mother killed in accident; Case 5, unmarried, secondary syphilis, anxiety over illness and pregnancy.

Of the 16 cases which occurred during the puerperium, 5 developed symptoms immediately after childbirth. Of the remainder, 2 developed during the second month of the puerperium, 3 during the third month, 1 during the fifth month, and 4 during the sixth month. The onset of the disease in the other case was at the end of the puerperium in the ninth month. The disease danger zone, therefore, so far as the puerperium is concerned, would appear to extend well into the sixth month, though the most potentially dangerous period is undoubtedly immediately after childbirth.

On the other hand, judging by the data in the series of pregnancy cases, there is little evidence to suggest that any one stage of pregnancy is more dangerous than another. The incidence was slightly greater in the third and fourth months than at other times. Cases, however, actually occurred in every month of pregnancy except the second.

A consideration of the histories of these patients suggests that the changes during pregnancy and the puerperium predispose rather than actually excite the disease, for other exciting factors, such as were found in the majority of the rest of the patients, were almost invariably present. The most likely explanation of the phenomenon would seem to be that during these events an increased susceptibility to unfavourable stimuli is acquired.

From this point of view, the puerperium would seem to be a more dangerous event than pregnancy, though the greater incidence, 16 cases as against 8, could also be explained by the greater chances of anxiety and sepsis during this time. A difficult confinement, puerperal sepsis, anxiety over the illness or death of the child, were the factors responsible for the present cases.

The factors underlying the suggested increase in susceptibility during pregnancy and the puerperium are unknown. It may perhaps in some way be a result of the increased excitability of the nervous system in general, or of the

autonomic nervous system in particular, which is a characteristic of these times. A heightened activity of the thyroid may also perhaps be another factor. In any case, whatever the mechanism ultimately proves to be, there can be little doubt that Fraser and Eason are correct in their view that these events are important aetiological factors in primary Graves' disease.

Before considering the next group of patients, there is one other interesting observation which can be made on these 29 cases developing during pregnancy and the puerperium, namely, that 15, or 52 per cent., were primiparae.

Ripmann, quoted by McCarrison (5), has drawn attention to the liability of primiparae to be affected by simple thyroid swellings during pregnancy, but there do not appear to be any definite observations on this point in the cases of Graves' disease. The explanation may be that these individuals are the subjects of an inherited neuro-endocrine instability, which is readily upset by the stresses of the first pregnancy. It could certainly be understood that anxiety and shock would be more potent factors in women who had had no previous experience of this event.

A study of the past histories of the other 42 married women who developed the disease at times other than pregnancy or the puerperium tends to confirm the view that these individuals are abnormal, for 33 per cent. had had no pregnancy prior to the onset of the disease. In several there was a history of sterility without apparent pelvic cause. Others were unable to face the ordeal of childbirth. A further 31 per cent. had had only one previous pregnancy. The incidence of previous pregnancies is therefore low in individuals who develop Graves' disease during the child-bearing period, suggestive evidence that they are abnormal either in constitution or outlook.

Relationship of the Climacteric to the onset of Graves' Disease.

There remains to be considered the group of 21 cases which occurred at or about the time of the climactic or afterwards. Of these, 13 developed within twelve months of this event and 3 in the years immediately following. The remainder, 5, developed after a sufficiently long interval to warrant their inclusion in a post-climacteric group. For the purposes of the present discussion, however, this further subdivision has not been considered necessary.

Before discussing the factors which are responsible for this high incidence at the time of the climacteric, it should be mentioned again that the clinical picture in these patients differs from that of typical primary Graves' disease as seen in earlier life. The thyroid swelling is generally slight and the gland harder, more compact, and less vascular than in the ordinary form. The eye signs also are not so prominent, though the thyroid intoxication and cardiac disturbance are relatively more severe. On the whole, the picture is more suggestive of secondary Graves' disease, though in all these cases symptoms of intoxication were present from the outset.

Let us now consider the relationship of the climacteric to the incidence of

the disease. The figures in the present series of cases strongly support the view that the climacteric is a dangerous event. The details of the present cases have been summarized in Chart E, which also gives information as to the extrinsic exciting factors, when such were present.

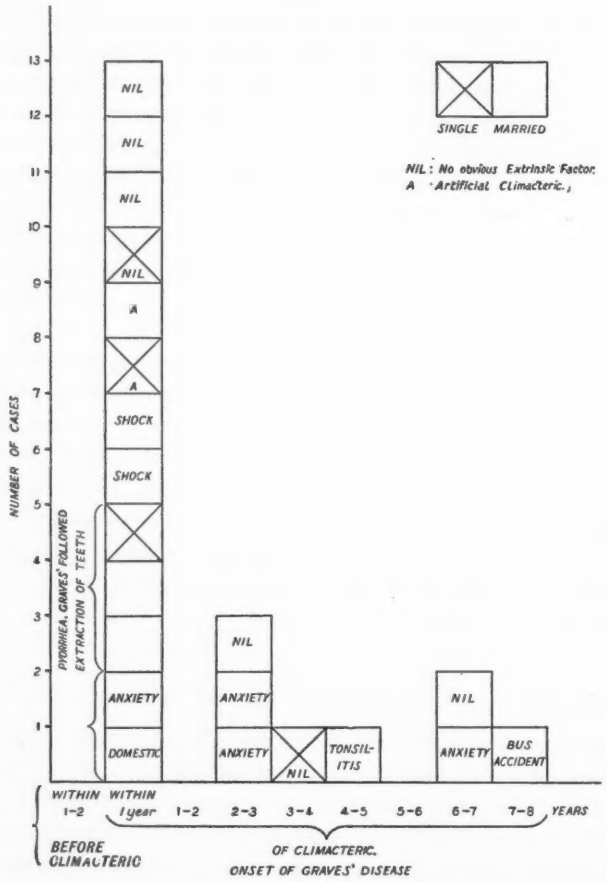


CHART E. Relationship of climacteric to onset of Graves' disease.

The high incidence at the time of the climacteric is striking, for 13 of the 21 cases developed within twelve months of this event. This incidence is out of all proportion to that in the years immediately adjoining, for in the preceding sections it was shown that up to the age of the climacteric the incidence of cases showed a gradual but steady decline, and afterwards, as will be seen in Chart E, the incidence is almost negligible.

To what, then, is the high incidence at the time of the climacteric due? The possibilities are twofold. It may be that the psychological changes which occur at this time are important factors, or the increase in incidence may be in some way related to the intrinsic changes associated with the climacteric itself. The

first possibility does not seem to provide an adequate explanation of the present series of cases, for whilst in two-thirds the individual factors were identical with those given in other groups and not in any way specific to the time of the climacteric, in one-third no obvious extrinsic factor could be found. The possibility of mental stress, however, cannot be entirely excluded, for the 'change of life' is known to be associated with anxieties which are not readily acknowledged.

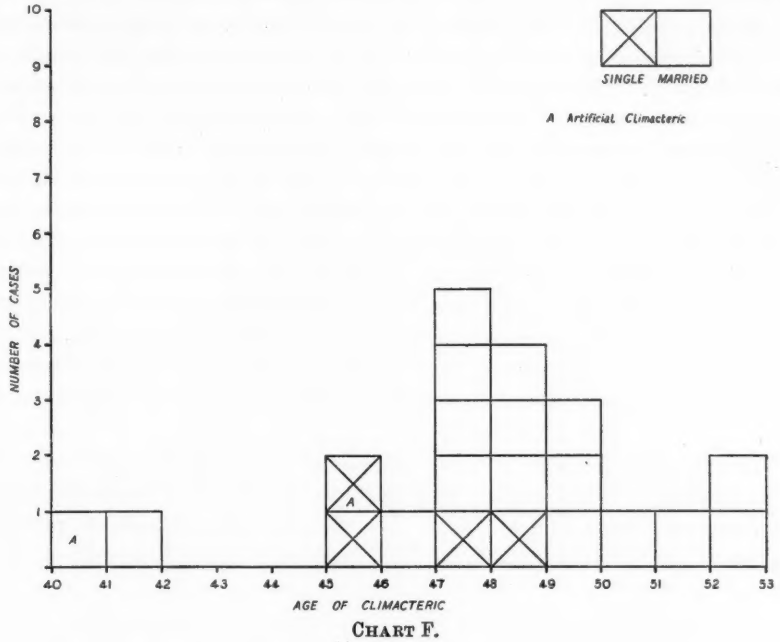


CHART F.

The second possibility is perhaps more likely—that the high incidence of cases is in some way related to the intrinsic changes of the climacteric itself. In the first place, it should be mentioned that in all but one of these patients the climacteric preceded by a short interval the onset of the disease. There is little evidence, however, to show that it was in any way abnormal, either from the point of view of age of occurrence or mode of termination. Details as to the age are given in Chart F.

This chart requires little further comment, except to point out the few cases in which the event was abnormal. In two patients, for instance, an artificial climacteric was induced by operative measures, hysterectomy and ovariotomy, at the ages of 40 and 45 respectively. Symptoms of Graves' disease developed in these patients almost immediately afterwards. In a third patient in whom the climacteric also occurred early, at the age of 41, menstruation never returned after the birth of the last child. There was no relationship, however, between the climacteric and the onset of Graves' disease in this case, for the latter developed after a bus accident twenty years later, at the age of 61.

On the whole, the age of the climacteric was slightly earlier in the single women, the average in four cases being 46 as against 48 in the seventeen married women. The difference, however, is very slight, and it may be assumed that, except in the abnormal cases mentioned, ovarian activity continued until the normal age and declined in a normal and natural way in all these patients. The influence of intrinsic changes in producing the high incidence at the climacteric is not, therefore, apparent from a study of this aspect of the problem.

There remains to be considered the possibility that underlying changes in the neuroglandular system, such as have been postulated during pregnancy, are the chief factors. Their influence again may be mainly predisposing and as such increase the susceptibility to an unfavourable environment at this time. This view would to some extent account for the preponderance of cases in married women, a proportion of 4 : 1 in the present series, for it is understandable that the ebb and flow of activity in the neuro-glandular system of the married woman would continue until a later age owing to the incidents of the active sex life and especially to repeated pregnancies. Such factors may quite possibly have played a part in the aetiology of the present series of cases, for practically all of them had had a number of pregnancies and up to a comparatively late age. If the actual figures as to the number of pregnancies in these climacteric cases are worked out, it is found that 72 per cent. of them had had two pregnancies or more.

This hypothesis is not offered as any solution of the problem as to why the incidence of cases is so high at the climacteric, but it will serve to emphasize that this event can be brought into line with the other sex events, puberty, pregnancy, and the puerperium, as important aetiological factors in Graves' disease.

Discussion.

The observations on this series of 206 cases make it possible to form an opinion as to the influence of the various events of the female sex life as aetiological factors in primary Graves' disease. The general conclusions which can be drawn are fully in keeping with those of other observers, namely, that the most important factors in precipitating the disease are shock, worries, mental strain, and infections, whilst adolescence, pregnancy, the puerperium, and the climacteric are undoubtedly dangerous events.

This expression of opinion is based on the following data:

(1) *Extrinsic factors*, psychic trauma and infections, apparently played an important part in the onset of the disease in 80 per cent. of the cases. Psychic trauma alone, shock or anxiety, precipitated the disease in about 50 per cent., whilst infections alone, chiefly tonsillitis and influenza, were the apparent cause in 20 per cent. In a further 10 per cent. psychological and toxic factors were present together. On the other hand, in 20 per cent. of the cases no extrinsic factor could be elicited in the history. This latter figure remained fairly constant throughout the various age groups considered, if the climacteric cases are excepted.

(2) *Intrinsic factors*, the sex events, are also judged to be important, for the incidence of cases at these times is considerably greater than at others. Moreover, in the present series of cases, as in others reported, the incidence of the disease was almost entirely limited to the period of active sex life, for only 1 case occurred before puberty and only 5 after the climacteric.

Of the 32 adolescent female cases, 30 per cent. developed in the same year as the onset of menstruation at puberty, whilst 56·6 per cent. occurred within three years of this event. Of the 71 cases in married women between the ages of 20 and the climacteric, 29, or 41 per cent., developed in direct relation to the events of pregnancy or the puerperium. Finally, of the 21 cases occurring at the time of the climacteric or afterwards, 62 per cent. developed in the same year as the offset of menstruation, and 76·2 per cent. within three years of this event. In all but one of these cases the climacteric was the prior event.

To summarize these observations, it may be stated that of the 183 female cases, 62, or approximately one-third, developed symptoms of Graves' disease within a sufficiently short interval of the sex events to justify the opinion that the latter had a considerable influence as aetiological factors.

A study of these statistics can leave little doubt that both extrinsic and intrinsic factors play an important part in the aetiology of Graves' disease, though it is perhaps difficult to form a definite opinion as to their respective spheres of influence. In many instances there is no doubt a considerable amount of overlap. The sex events, for example, and notably pregnancy and the climacteric, are not only associated with important intrinsic changes, but are also times of considerable mental stress.

On the whole it would seem most likely that the first group of pathological influences play the part of *exciting* factors, whilst the influence of the physiological sex events is rather of a *predisposing* nature, with the result that during the active sex life in general, or any of its events in particular, the susceptibility to pathological influences is increased.

Judging by the curves in Charts A and B, the latter group of intrinsic factors play the more important part in colouring the incidence picture of the disease. The almost complete limitation to the period of active sex life and the tendency to increased incidence at times corresponding to the sex events are most suggestive. These points will be seen if reference is again made to the charts. In the two curves, there are three main *peaks* of maximum incidence; the first in girls and single women between the ages of puberty and 24; the second in married women between 25 and 42; and the third in married women about the time of the climacteric. In single women, on the other hand, after the age of about 24, the incidence decreases and remains at a relatively low level, even at the time of the climacteric.

Apart from the undoubted influence of intrinsic changes in producing the high incidence during puberty and adolescence, there is also most probably another factor, namely, that it is during these years that exposure to extrinsic stresses, both psychological and toxic, occurs to a large extent for the first time.

There is also another probability which must be considered, that many of these individuals have an inborn tendency to the disease, and few pass through the stresses of adolescence and early adult life without acquiring it. This may to some extent account for the decreasing incidence in single women in later life, though another reason for this is probably their attainment of a greater degree of nervous and glandular stability.

The relative frequency, on the other hand, of Graves' disease in married women would appear to depend on the acquisition of a further 'predisposition' to the disease. This seems to be mainly dependent on the intrinsic changes associated with their more active sex life, and especially such events as pregnancy. The first 'peak', for instance, between the ages of 25 and 42, is largely due to the high percentage of cases which developed during pregnancy and the puerperium. The fact that so many of them developed the disease in early married life, or in connexion with their first pregnancy, is perhaps additional evidence that they are the subjects of some constitutional inadequacy, though it is probably a grade less than that of the adolescents and young adults who acquire the disease earlier. The second 'peak', on the other hand, in married women in later life appears to coincide with the events of the climacteric. The most likely explanation of the higher incidence in married women at this time seems to be that there is a greater and more prolonged activity in the neuro-glandular system in their case.

A discussion of the underlying neuro-glandular changes during the active sex life and at the times of the sex events is not within the scope of this investigation, even if it were possible. There are, however, two points which arise from these observations which require brief mention. The first is that ovarian activity in the present series of cases did not appear to differ in any way from that in the normal person. Puberty occurred at the normal age in the large majority of adolescent cases, and in 80 per cent. of these girls the course of menstruation was quite normal and regular before the disease began. The events at the climacteric were also of a normal type in all but two or three of the climacteric cases, and there was no reason to suppose that disturbances of menstruation or ovarian activity played any part in the onset of the disease in the other cases.

The second point is connected with a recent investigation of Cooper's. This worker has studied by histological methods the activity of the more important endocrine organs at different times of life in the normal person. Her conclusions as to the activity of the human thyroid are as follows:

Throughout infancy and childhood secretory activity is marked, but the gland always maintains a small amount of colloid in its vesicles.

At puberty, the demand for this internal secretion is at its height, and the gland, though secreting to its greatest extent, is unable to store up any appreciable amount of colloid.

During adolescence the thyroid attains its maximum size and has the appearance histologically of a hyperactive gland. The resemblance to the

histological picture described as characteristic of exophthalmic goitre is both striking and significant.

By the 20th year the activity of the gland seems to have abated, judging from histological appearances, and throughout adult life it would seem able to enjoy a period of comparative inactivity.

A thyroid gland, however, obtained from a *pregnant* woman of 37 years of age showed signs of increased activity.

In the latter part of life the thyroid body shows a reduction in size and, judging from histological appearances, a diminution in function.

Towards the 50th year the thyroid seems again to attempt further activity, but this is not marked.

Finally, *in old age* there are retrogressive changes.

Cooper's conclusions have been quoted fully, because they show that there is a striking resemblance between the curve of thyroid activity in the normal person and the incidence curve in the present series of cases of Graves' disease. This raises the possibility that the state of activity of the thyroid may be one of the underlying factors which accounts for the peculiar incidence of the disease.

This hypothesis may throw some light on the predisposition to the disease which is apparently present during the active sex life, but it does not help to elucidate the problem of the Graves' disease 'diathesis' or explain why it is that these individuals react to stimuli so abnormally.

For, when all is said and done, this abnormal reaction to unfavourable stimuli is the only apparent outstanding difference between these and normal persons. The pathological influences and physiological events, which appear to have been such important aetiological factors, are circumstances which, even when they occur together, the normal individual can survive without any difficulty.

Conclusions.

1. 206 cases of primary Graves' disease have been studied with special reference to the significance of the sex events in their aetiology. Of these cases, 183 were females and 23 males, a ratio of 8 : 1.

2. Of the 183 females, 32 were adolescent, 63 single, and 88 married women. Of the males, 6 were adolescent, 4 single, and 13 married men.

3. The incidence of the disease was almost entirely limited to the period of active sex life, only one case occurring before puberty and only five after the climacteric.

4. In 80 per cent. of these cases the disease was precipitated by extrinsic factors, shock, mental stress, and sepsis. In 50 per cent. the two former factors, in 20 per cent. the latter, whilst in 10 per cent. they were combined. In the remaining 20 per cent. there was no apparent extrinsic exciting factor.

5. The sex events in the female—puberty, pregnancy, the puerperium, and the climacteric—appear to be important predisposing factors, for the incidence of cases was considerably greater at these times. Of the 183 females, 62, or approximately one-third, developed the disease at the time of these events.

6. 30 per cent. of the adolescent and 62 per cent. of the climacteric cases developed the disease in the same year as the onset and offset of menstruation respectively. 56·6 per cent. of the adolescent and 76·2 per cent. of the climacteric cases developed the disease within three years of these events.

7. Of the 71 cases in married women during the child-bearing period, 41 per cent. developed the disease during pregnancy, the puerperium, or after miscarriage. The incidence during the puerperium was double that during pregnancy.

8. Of the 71 cases in married women during the child-bearing period, 14, or 19·7 per cent., had had no pregnancy prior to the onset of the disease; 13, or 18·3 per cent., had had only one pregnancy; and 15, or 21·1 per cent., developed the disease during their first pregnancy or puerperium.

9. Of the 21 climacteric cases, 17 were married and 4 single. 72 per cent. of the former had had two or more pregnancies. The low incidence of cases at the climacteric in single women is in keeping with the general decrease in incidence in single women in later life.

In conclusion, I wish to express my thanks to Professor Hugh Maclean, the Director of the Medical Unit, St. Thomas's Hospital, to the members of the Staff of St. Thomas's Hospital, and to the Medical Research Council for the facilities they have given me for carrying out this investigation.

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THE CAUSES OF AURICULAR FIBRILLATION[1]

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With Plates 8 and 9

AURICULAR fibrillation is one of the most common disorders of the heart, but we have, as yet, little knowledge of its causes. It is more common in men than in women, and after forty, though it may occur at any age. It is frequently associated with mitral valvular disease, and infrequently with aortic lesions. It is common in chronic myocardial disease, and uncommon in acute infections. It is often present in cases of exophthalmic goitre; and it may occur, occasionally, in any form of heart disease; and, rarely, in patients whose hearts are apparently sound.

It is in many ways a curious affection. In some cases it continues after its onset, until the end of life, though this may be delayed for many years (12 (22), 12 (6), 14 (9), 15 (20)). In others it occurs in paroxysms, of very variable duration—seconds, minutes, hours, or days. The paroxysms may recur frequently or infrequently. One of our patients was fibrillating for seventy out of seventy-eight days in hospital. Another had as a rule a regular pulse though her attacks were numerous, as these were of short duration, the longest lasting for some twelve hours and the shortest but a few minutes. Paroxysms, too, may only appear at rare intervals. One patient had his first attack in 1920, and his second in 1927, unless some short paroxysms of 'palpitation' in the summer of 1922 were due to this cause.

It seems reasonable to suppose that fibrillation must be due to several causes. The paroxysmal attacks must surely own a different origin than that which produces the permanent disturbance.

In 1913 A. M. Gossage and J. A. Braxton Hicks (16) suggested that the causes of fibrillation must be varied. They conceived that it might be due to: (1) some definite morbid condition of the muscle-cells; or, (2) some extrinsic stimulus such as a blood poison; which, while (*a*) more likely to influence an already damaged organ, might also, (*b*), if sufficiently strong, produce fibrillation in a healthy heart. The evidence which is now available seems to support their contentions.

[1] Received September 12, 1928.

Auricular Fibrillation associated with Pathological Lesions in the Auricular Muscle.

Auricular fibrillation is most frequently associated with mitral valvular disease and those cases of cardiac failure due to disease of the coronary arteries, in both of which structural alterations in the cardiac muscle are the rule. In mitral disease the auricular muscle is but rarely unaffected, and it is in this group that fibrillation is most common. One often sees in the post-mortem room large dilated auricles with fibroid walls and scanty muscle-cells, so few and far between that it must have been impossible for co-ordinate contractions of the auricle to occur, or for the passage of stimuli in such regular even fashion as would offer to the ventricles a regularly recurring efficient stimulus. Pl. 8, Fig. 1, for example, which was obtained from a patient whose auricles were found on post-mortem examination to be enormously dilated, shows little, if any, signs of auricular activity.

There is still a scarcity of observations upon the condition of the auricular muscle in auricular fibrillation, but fibrosis of the auricles has been reported frequently (1, 3, 8, 19, 11, 21, 22, 27, 33). Carey Coombs and Herapath (5) have examined eighteen cases in some detail. In *all* of these cases the auricular muscle, as gauged by the presence of fatty changes, was grossly damaged, while changes in the ventricular muscle were comparatively slight. In twenty-six control cases, in which the auricles were not fibrillating, the auricular and ventricular muscle was equally affected. In three chronic cases with gross damage to the auricular muscle the auricles were not fibrillating, and in one acute case, also with gross auricular damage, fibrillation was also absent.

It thus seems probable that severe damage to the auricular muscle may occasion fibrillation.

In the acute infections inflammatory changes in the cardiac muscle are not uncommon, but they are usually most severe in, and sometimes wholly confined to, the ventricular walls. They are most common in acute endocarditis, acute rheumatism, diphtheria (4, 6, 13, 26, 31). Auricular fibrillation is uncommon in the acute infections, but has been reported to occur in acute endocarditis (4, 6, 21, 22, 29, 31), acute rheumatism (22, 29, 30, 31), diphtheria (24), influenza (32), pneumonia (27, 22), pneumonia with pericarditis (19).

It seems probable that the infrequent occurrence of fibrillation in the acute infections is due to the relatively slight involvement of the auricular muscle in these diseases, during the acute stage. In the later stages of rheumatic valvular disease fibrillation is frequently present, the incidence increasing rapidly after the age of thirty (5).

It is well known that, in the acute infections, heart block, partial or complete, may occur, and that, with recovery and healing of the myocardial inflammation, the disturbance of the rhythm may pass away. A comparable lesion in the auricular muscle would explain the temporary occurrence of fibrillation. We can only find one reference (33) to the condition of the cardiac muscle in a case

of paroxysmal fibrillation. In this the muscle showed fibrosis and lymphocytic infiltrations, the latter being, in part at any rate, of recent origin.

Auricular Fibrillation associated with Intoxications (a).

The frequent occurrence of auricular fibrillation in Graves' disease suggested that an examination into this association might prove helpful, for Graves' disease is due to an intoxication. But the data, on investigation, are confusing.

It is difficult to estimate the true incidence of fibrillation in this disease, for all statistics are based upon hospital records, and so on the more severe and protracted cases. Of these, 5–10 per cent. are fibrillating. Graves' disease frequently follows an acute infection such as acute rheumatism or tonsillitis; or occurs in a patient who had had one of these diseases, or chorea; and is thus not unlikely to have a damaged heart.[2] Towards the termination of the illness, too, infections of very varied kind are not uncommon, and necessarily obscure the picture. Lesions found *post mortem* in these cases are thus not necessarily the sequel of the Graves' disease, though they may be, in part at any rate, the cause of the fibrillation. Many lesions have been found, fatty changes, necrosis of muscle-cells, acute myocarditis, fibrosis, &c. In some instances these are evidently so recent and so acute that they must have succeeded the onset of the fibrillation and could not have been its cause.

The experimental evidence, however, makes it clear that hyperthyroidism has an injurious influence upon the heart (17). Continued feeding with thyroid gland causes, in rats, an enlargement of the heart, and, if large doses are given, death within two or three weeks. In these animals, infiltrations of cells round the blood-vessels of the heart seem to be invariably present. The cells are mainly of connective tissue origin, with some lymphocytes. If the lesion is small the adjacent muscle-cells are little altered, but if large the muscle-cells show various degenerative changes, with ultimate disappearance of the cell. Fatty

[2] *Exophthalmic Goitre.*

Age.	Male.	A. F.	Female.	A. F.	
1–9	—	—	—	—	
10–19	2	—	4	—	
20–29	1	—	19	—	
30–39	3	—	15	5+1 (paroxysmal)	
40–49	4	1 (paroxysmal)	12	3+1 (paroxysmal)	
50–59	2	—	3	2	
	—	—	—	—	
	12	1	53	12	= 65 cases

	Cases.	A. R.	Tonsillitis.	Chorea.
A. F.	13	2	3	—
Not A. F.	52	10	14	2
	—	—	—	—
	65	12	17	2

In this series of hospital patients 13 cases showed auricular fibrillation, but none of these were under thirty years of age. The incidence of acute rheumatism, tonsillitis, and chorea are shown in the second table.

changes do not seem to occur. If these changes were severe in the auricles they might be the cause of fibrillation, quite apart from any intoxication.

But one point has emerged from the investigation. It has been shown that, in many cases of exophthalmic goitre, fibrillation, if present, ceases after the removal of a part of the thyroid gland. Thus, in a series of 75 cases, watched for three to six months after operation, fibrillation ceased in 43 cases (25). In another series (9), carefully checked with the electrocardiograph, fibrillation ceased spontaneously in 8 cases, and after the administration of quinidine in 9 cases, persisting in but 2 of the series. The chief factor in the cases which recovered seems clearly to have been the intoxication, for with removal of part of the gland the fibrillation ceased.

Auricular Fibrillations associated with Intoxications (b).

There is also evidence that auricular fibrillation may be produced by an intoxication acting on a healthy heart.

In the *laboratory*, in animals, fibrillation can be readily produced in many ways. It is easily excited by electrical stimulation. It may follow the administration of digitalis (7), potassium bromide, adrenalin (27), potassium chloride, calcium chloride, barium chloride, chloral hydrate, camphor, &c. But the results are uncertain. 'Chloral hydrate sometimes produces fibrillation, but also will neutralize the action of digitalis, and prevent fibrillation (Gley, Berbera). Camphor, it is claimed, makes the induction of fibrillation more easy, and the recovery from this state more difficult (Klemperer), but, on the other hand, it is held that camphor stops fibrillation (Seligman, Gottlieb, Magnus). In these conflicting reports one sees that it depends upon dosage and localization of action whether the drug favours, or is inimical to, fibrillation.' (Garrey (15).)

Fibrillation may also follow the ligation of a coronary artery (21).

On the *clinical* side comparable cases have been reported, and it has been stated to follow the administration of digitalis (7, 22), general anaesthetics (19), sulphuretted hydrogen (28), and coal gas poisoning (4).

There is again a scarcity of observations on the histology of the heart in such cases, but Gossage (16) has reported a case in which fibrillation had been present for at least eighteen months prior to death, whose heart, on microscopic examination, seemed to be quite normal.

There is thus a considerable amount of evidence in favour of the thesis which was enunciated by Gossage and Hicks. Gross chronic lesions have been found in many hearts which, prior to death, showed permanent auricular fibrillation; and in one case of paroxysmal fibrillation chronic and acute lesions were present. It seems reasonable to suppose that these pathological lesions were the cause of the disorder.

On the other hand, in one case of fibrillation the cardiac muscle, examined after death, seemed to be normal; and, experimentally, fibrillation is readily

produced by the administration of various poisons, acting upon a healthy heart. It seems reasonable to suppose that an intoxication may produce fibrillation in man as well as in animals. The following clinical records seem to support this contention.

Clinical Records.

Two cases have been reported in which auricular fibrillation ensued as the result of an *electrical shock*. In one case (18) the patient was a healthy man, aged 35, and the irregularity immediately succeeded exposure to a direct current of about 250 volts for a couple of minutes. The heart seemed to be normal save that the apex impulse during the continuance of the fibrillation was slightly displaced outwards. Treatment by quinidine restored the rhythm to normal and the patient was able to resume his previous, moderately heavy work. The fibrillation, however, tends to recur, though the attacks are readily controlled by quinidine. The second case (10), was that of a man aged 24, who, although he had a very large heart accompanying double mitral disease, was able to play football, cycle, &c., and keep in regular work. One day he received a high voltage shock, and from that moment began to be short of breath, which, gradually increasing in severity, forced him to take to bed three weeks later. The auricles were then fibrillating. He has been unable to work since the accident.

The association of *trauma*, or *physical exertion*, and auricular fibrillation is so constantly brought to our notice by our patients that the association needs little stress. As we write, a patient informs us that her first attack of fibrillation succeeded 'spring-cleaning' some years ago. Her present attack, which appears likely to be permanent, commenced one evening last autumn when she was walking home from the railway station, up hill, carrying a heavy parcel.

Cassidy (2) has observed fibrillation in a healthy man, aged 46, which ensued one day after a vigorous game of tennis on a hot day, followed by a plunge into the sea. The fibrillation ceased spontaneously five days later, and now, four years later, has not recurred, though the electrocardiogram shows a progressive change suggestive of myocardial damage. Mackenzie (22) states that 'effort, sometimes slight, sometimes violent, may provoke auricular fibrillation'. Emanuel (10) states that 24 out of 52 patients associated the onset of their fibrillation with some muscular effort. John Hay (19) has recently emphasized the frequency of the connexion. It is true that in the majority of these patients the heart is obviously, or probably, not quite sound, but in some instances the organ shows no other abnormality, and in Gossage's (16) case, that of a man aged 23 whose irregularity succeeded an attack of cough, a careful microscopic examination after death failed to reveal any pathological changes in the muscle.

Many patients ascribe the onset of their complaints to *indigestion*, or some form of *gastro-intestinal disturbance*, and many writers have noticed the connexion. Vaquez (32) has reported its occurrence after a hearty meal.

Wolferth (34) mentions a case of transient fibrillation which occurred in the course of an attack of acute appendicitis. Felberbaum and Finesilver (12) have recorded several cases. One patient, a woman aged 65, who suffered from attacks of hepatic colic, had four seizures between 1917 and 1924 each of which was followed by an attack of fibrillation. Her fifth attack was associated with acute cholecystitis, and, during a temporary improvement in the second week, fibrillation ensued and persisted. Under quinidine it changed into flutter, but after the administration of digitalis the fibrillation returned and continued until her death two weeks later. Another patient had an attack of fibrillation during a temporary, but severe, attack of colic. Another patient had recurring attacks of fibrillation while under treatment for duodenal ulceration. Another, who had mitral stenosis, the sequel of chorea in early life, had attacks of fibrillation during an attack of acute appendicitis, the irregularity ceasing when the appendix had been dealt with by surgical methods.

Cassidy (2) has kindly furnished us with notes of another comparable case. A healthy man, aged 52, accidentally ate about six grains of arsenic. Vomiting and diarrhoea at once ensued, and he was found, two hours later, lying on the floor, unconscious, pulseless, collapsed, and apparently dying. Auscultation showed that the auricles were fibrillating, the ventricles beating at about 180 per minute. The fibrillation ceased after twenty-four hours, the systolic blood-pressure being then 80 mm. Hg. He has made a complete recovery, and the fibrillation has not recurred, six years later.

A series of similar paroxysmal cases which came under our observation last autumn attracted our attention to the connexion.

Case 1. The patient was an active man aged 53. He had played football in his early years with success, and had always enjoyed good health. On one occasion, two years prior to the present attack, he had hurried on his way to an international football match, after lunch, and had become so short of breath upon the way that he had hardly been able to walk up the stand to his seat. But the discomfort soon passed, and he paid no attention to it. He may have had transient attacks of palpitation subsequently, but these were so slight and of such short duration that he paid no attention to them. One morning he took a dose of salts which acted freely after his breakfast, and he then walked down to his office, about half a mile distant. As soon as he reached it, about 10 a.m., an attack of palpitation ensued, accompanied by a call to stool. He felt very ill and was scarcely able to reach the lavatory. The bowels again moved very freely, and he then helped himself to some whisky and collapsed on to a sofa. When seen by his doctor, about 11.30, he was very collapsed with a frequent almost imperceptible irregular pulse. After free stimulation he rallied, and he was removed home after five or six hours. When we saw him, about 8.30 p.m., he was still very weak, with a small, soft, frequent pulse, the rate being about 130. The auricles were clearly fibrillating. Two hours later the pulse-rate was about 100, and the quality had improved. Next morning the fibrillation persisted, but the rate had fallen to 80–90 and his general condition had improved. In the afternoon he fell asleep, and when he woke his pulse rate and rhythm were normal. His subsequent progress was satisfactory. The only abnormality which was detected was some slight splintering of R III when an electrocardiogram was taken six weeks later (Pl. 8, Fig. 2). His blood-pressure at this time was 140 mm. Hg.

Case 2. The patient, who is now aged 67, had his first attack of fibrillation eight years ago. He said that he had been getting more short of breath on exertion for some years, but he had not paid any attention to his discomforts, and carried on at his work. One morning he had a loose stool after breakfast, and about 10 a.m., while walking upstairs, was suddenly seized with a sense of constriction in his chest, and became extremely short of breath. When seen, about 2 p.m., his auricles were fibrillating, but after he had undressed and laid down on the couch his pulse became quite regular. Occasional extra-systoles occurred at this time. Two years later he was becoming more short of breath, and had attacks of palpitation and breathlessness at least every month. One attack occurred two hours after a very free evacuation of the bowels, and he paid us a visit in the afternoon, but his pulse was then quite regular. His subsequent progress was good and the attacks did not recur until the summer of 1927, when he had an attack which lasted for twelve hours.

On all these occasions the attacks were associated with gastro-intestinal symptoms. He was a large feeder and took large quantities of fluid with his meals, which produced flatulence. He tended to be costive and, in consequence, took large doses of laxatives from time to time. His first and second attacks were associated with very free movements of the bowels, following medicine. His last attack supervened about 5 a.m. He had eaten, late at night, a very large meal of fried eggs and ham, &c., and had been disturbed by several professional calls during the night. In each instance care as to his diet led rapidly to the disappearance of his cardiac discomforts, which remained absent so long as he adhered to his restrictions. His wife was quite clear that his palpitation was always due to careless habits of feeding, and to the ingestion of large quantities of tea, &c., at his meals.

When first seen, in 1920, little abnormal was detected on examination. He was rather flabby, and save that his left heart seemed to be a little large and that his radial arteries were just palpable, his organs seemed sound. The blood-pressure was 135–100 mm. Hg., the cardiac sounds were closed and of quite reasonable quality, and the electrocardiogram, taken ten days after his attack of fibrillation, was quite normal. There is still little abnormal to be detected. There is no enlargement further of the heart, the cardiac sounds remain pure. The blood-pressure is high, and now runs about 160–95 mm. Between 1922 and the spring of 1927, i.e. prior to his last attack of fibrillation, R III altered and now shows definite splintering, while the Q-T interval is also lengthening and now measures 0·38 in. as against 0·36 in 1920. He is still in active work, though he takes life a little more easily than of yore (Pl. 9, Fig. 3).

Case 3. The patient was an active man aged 58, whose sole complaint was of attacks of palpitation. He had been subject to these for at least ten years, and, when seen in one at the commencement by his doctor, was told that he had fibrillation and given a serious warning. The attacks were irregular in their occurrence, being sometimes very frequent, and sometimes infrequent. He might be free from them for a year or so at a time. Apart from these attacks he felt in good health and had no difficulty in carrying on his business. On one occasion he had had frequent attacks just prior to his summer holidays, and felt so unwell that he hesitated to leave home. But as soon as he reached his holiday quarters the attacks disappeared, and he played golf without any inconvenience. He was a well-built man and his organs seemed sound. His blood-pressure was 160–85 mm. Hg. The only abnormality detected was a prolongation of the Q-T interval, which measured 0·38–0·40 in. (Pl. 8, Fig. 4).

At the time of his visit his auricles were fibrillating, and the ventricles were beating at about 134. He did not, however, appear to be distressed. On his way home the paroxysm ended, and, when seen the next day, the pulse was regular and quiet. A second electro, taken a few days later, showed a normal rhythm.

His wife *laughed* at his attacks. He had had paroxysms for many years and was inclined to take the matter seriously, but she *knew* that it was all a matter of his diet. He was fond of pastry and sweet stuffs, and liked to drink large quantities of fluid at his meals. If he did this he became flatulent, and attacks ensued. His present attacks were the sequel to Christmas festivities! On Christmas day he drank several bottles of ginger beer and ate largely of the pastries provided for the children. His first paroxysms occurred on December 26, and they became more frequent on December 27 and the next day. On that evening she gave him a dose of castor oil, and the attacks ceased. Reasonable care as to diet, fluids, &c., was followed by disappearance of his attacks.

In these three patients a meticulous examination of the heart revealed minor deviations from the normal, but for all practical purposes the hearts did their work easily and well, and did not interfere with normal activity, save at the times when digestion was upset. Removal of the indigestion relieved the cardiac disorder. It seems probable that comparable intoxications, arising in other organs may, too, be the cause of fibrillation.

It thus seems clear that digestive disorders, whether organic or functional, may be the cause of auricular fibrillation. They may, conceivably, act in different ways; by flatulent distension of the abdomen displacing the diaphragm, and the heart, upwards; by altering the volume or the distribution of the blood as the result of vomiting, diarrhoea, or accumulation of the blood in the abdominal cisterns; or by occasioning an intoxication which acts directly upon the cardiac muscle.

It is well known that other disorders of the cardiac mechanism are frequently due to digestive disorders. Gastric flatulence is probably the most common cause of extra-systoles, and paroxysmal tachycardia is sometimes due to similar causes. Ritchie (27) informs us that each of the six attacks in one of his patients succeeded eating some unsuitable article of food. One attack, for instance, followed a meal of veal pasty, another a supper of boiled eggs, both of which, she knew, disagreed with her digestion. We have seen several cases in elderly people, subject to obstinate constipation and intestinal flatulence, in which attention to the digestion lessened the frequency of the attacks. In another case, attacks, which had been fairly frequent, practically ceased on the removal of a gall-stone which had become obstructed in the cystic duct.

Conclusions.

Auricular fibrillation is a disorder of the cardiac mechanism. *Permanent* fibrillation is probably due to pathological lesions in the auricular muscle. *Paroxysmal* fibrillation may be due to the action of various intoxications, which, while more likely to affect an already damaged heart, may apparently also affect a healthy organ. The prognosis in the two groups of cases is, in consequence, different.

The intoxication is sometimes of gastro-intestinal origin, and removable. From the practical point of view it is necessary to take a wide survey of the

case if the auricles are fibrillating, and to make sure that *every other organ is functioning well* before we lay the charge to the heart itself.

I have great pleasure in acknowledging the kindly assistance afforded to me by many friends: M. A. Cassidy, Carey F. Coombs, J. G. Emanuel, G. B. Fleming, F. R. Fraser, John Hay, G. R. Murray, W. T. Ritchie, A. W. Harrington, and J. K. Rennie.

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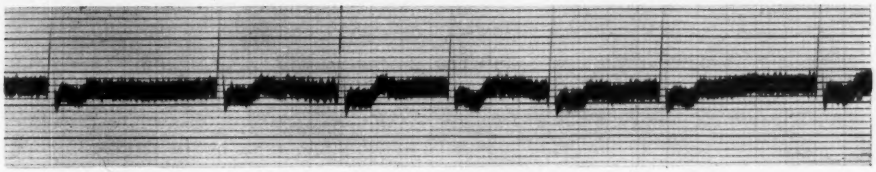


FIG. 1. Electrocardiogram from a patient whose auricles were enormously dilated

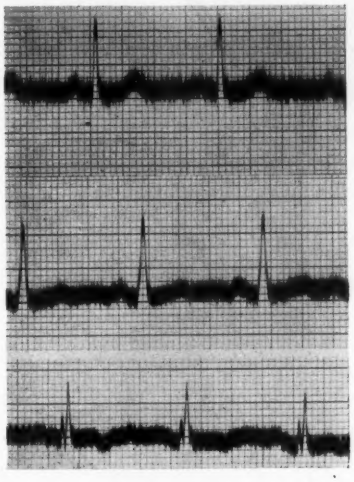


FIG. 2. Case 1. Electrocardiogram taken six weeks after the attack of fibrillation

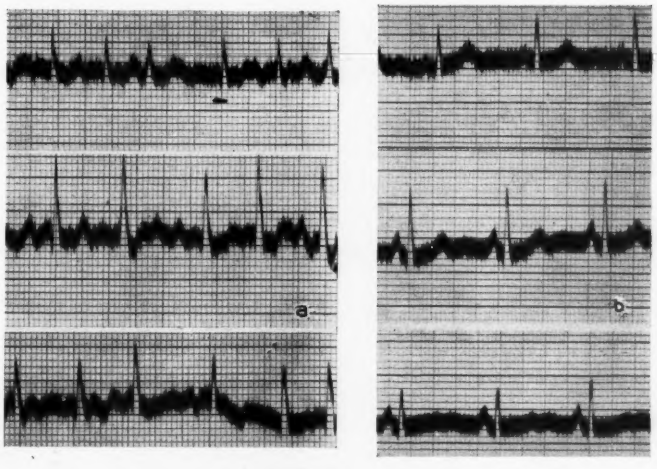


FIG. 4. Case 3. Electrocardiograms taken during a paroxysm of fibrillation (*a*), and about three weeks later (*b*)

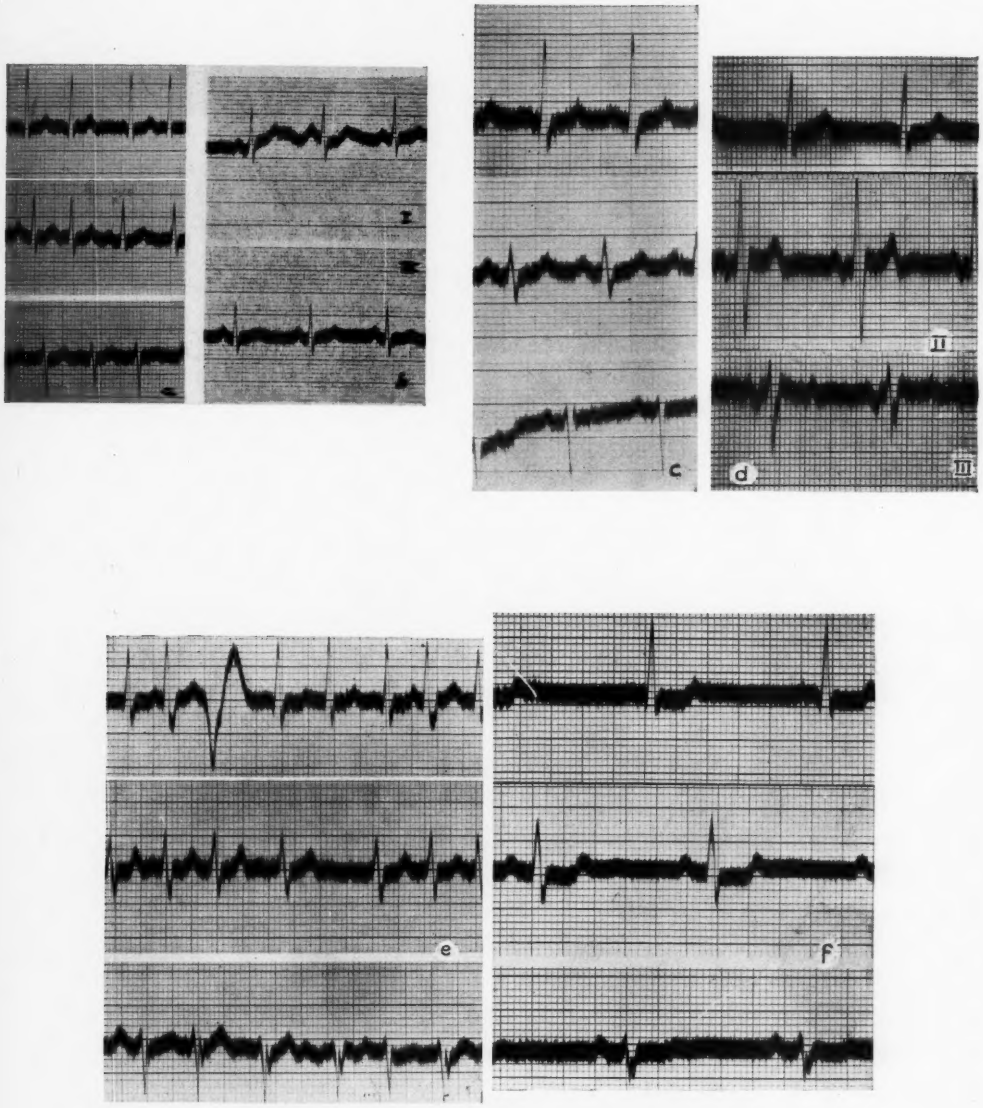


FIG. 3. Case 2. Electrocardiograms taken on 18. v. 20 (*a*), 27. v. 20 (*b*), 4. xi. 22 (*c*), 9. ii. 27 (*d*), 30. vii. 27 (*e*), 13. xii. 27 (*f*); showing auricular fibrillation in (*a*) and (*e*)

STEREOSCOPIC RADIOGRAPHY OF THE CORONARY SYSTEM[1]

By JOHN S. CAMPBELL

(From the Pathological Laboratory of the Royal Victoria Hospital, Belfast)

With Plates 10-16

THE minute anatomy of the vascular system is one worthy of close attention. Its study does much to present a clearer picture of the basis of many conditions which clinically are of the first importance.

A method is described by which radiography of organs removed shortly after death may be utilized to this end. Its primary aim is anatomical. Anatomical modifications due to age and disease are included, while clinical data are mentioned for the purpose of illustration.

No attempt is made to include a survey of the published literature, but comparisons and references are made where appropriate. The injection of blood-vessels with various coloured substances has long been practised in anatomical study. The development of the Röntgen rays suggested the use of opaque fluids, while more recently stereoscopic radiography has made possible a range of investigations as yet only in their infancy. Of these the coronary circulation has provided a most interesting research, and to it I have devoted the succeeding pages.

Technique.

A portion of the great veins must be removed intact with the heart. This is essential if troublesome leakage from the atrial vessels is to be avoided. Careful examination is made of the aorta, aortic cusps, and orifices of the coronary vessels, and the presence, or otherwise, of any accessory openings noted.

Opaque medium. Röntyum, a preparation of barium, was found to give the best results. This substance forms a very fine and stable emulsion. 40 grm. is emulsified with 75 c.c. of distilled water. This must be finely ground in a mortar, great care being taken to ensure good emulsification.

The apparatus illustrated (Fig. 1) enables a standard pressure to be maintained throughout the injections. A pressure of 280 mm. of mercury for three minutes

[1] Received July 9, 1928.

is used. The heart is washed out, removing all clots. The proximal portion of each coronary artery is exposed, and, on injection, ligatured close to the aorta. The heart is again washed. The chambers are packed with wool and the organ immersed in formalin 10 per cent. for 24 hours to secure fixation in the optimum position for stereoscopic examination.

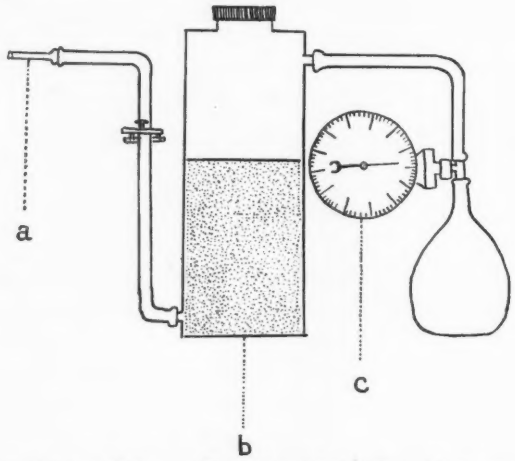


FIG. 1. (*a*) transfusion needle; (*b*) metal cylinder; (*c*) manometer.

This simple method has been found to give satisfactory pictures when a stereoscopic X-ray has been taken of the injected specimen. One week in formalin is necessary before separate portions of the heart are photographed.

The skiagrams demonstrate very clearly the finer ramifications of the cardiac vessels, while small variations in their calibre can be readily noted. A fuller interpretation of the skiagrams necessitates detailed knowledge of the minute anatomy of the cardiac circulation. The monograph by Gross (1) proved invaluable and forms the anatomical basis on which the present work is built.

The Distribution of the Coronary Arteries.

The left coronary artery (Fig. 2) arises from the left anterior sinus of Valsalva, below the level of the free edge of the aortic cusp. It is usually larger than the right. The main stem, which varies in length, runs forwards and to the left behind the root of the pulmonary artery under cover of the tip of the left auricle. It bifurcates practically at once into a ramus descendens anterior and a ramus circumflexus sinister.

The ramus descendens anterior courses downwards in the anterior interventricular sulcus, curls round the apex of the heart, and terminates at the twigs of the posterior descending ramus.

Rami marginales are given off to the anterior and lateral walls of the left ventricle. The first—as a rule the largest—of these may arise from the ramus

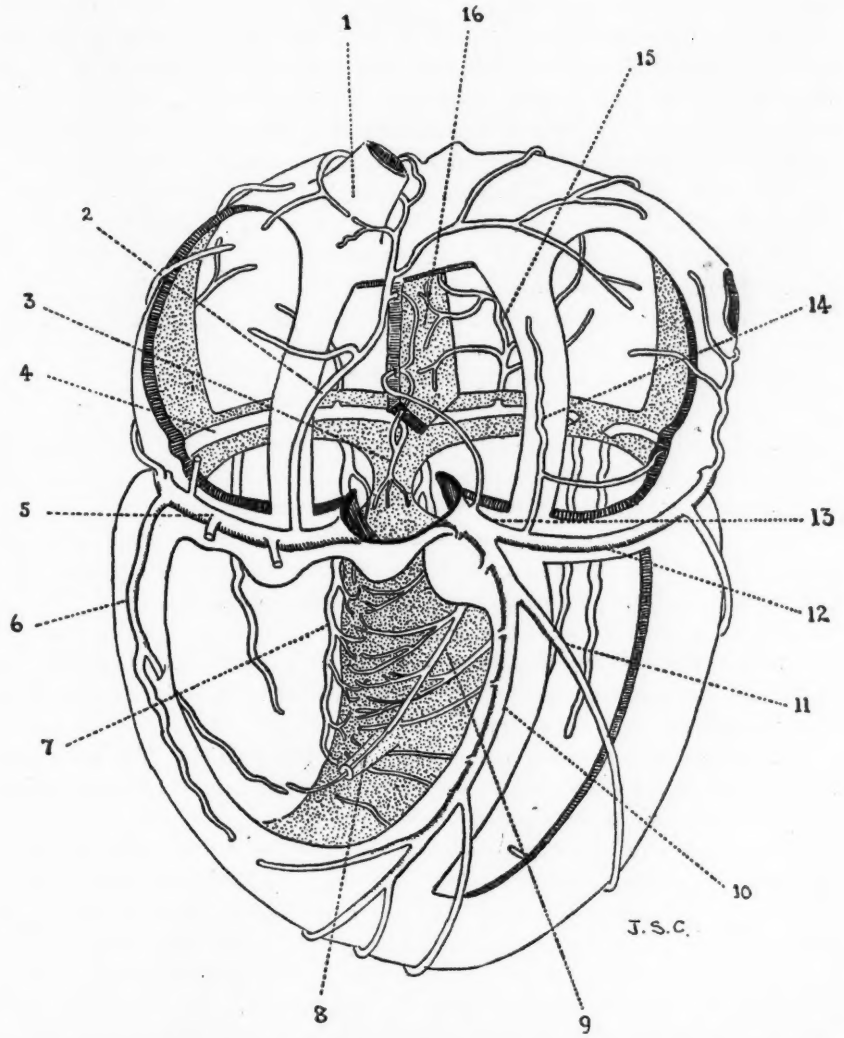


FIG. 2. 1, superior vena cava; 2, ramus ostii cavae superioris; 3, ramus septi fibrosi; 4, circumflex branch, right coronary; 5, right coronary artery; 6, ramus lateralis; 7, ramus descendens posterior; 8, artery in moderator band; 9, anterior septal vessel; 10, ramus descendens anterior; 11, ramus marginalis; 12, circumflex branch, left coronary; 13, left coronary artery; 14, ramus atrii sinistri anterior; 15, ramus atrii sinistri posterior; 16, interatrial septum.

circumflexus sinister. The anterior surface of the right ventricle receives several twigs.

The ramus circumflexus sinister lying in the atrio-ventricular furrow rounds the margo obtusus, and, gaining the posterior surface of the heart, turns downwards to supply a postero-lateral strip of the left ventricle.

These vessels lie on the surface of the heart. They are usually embedded in fat, and, in some places, bridged over by muscular strands.

The right coronary springs from the aorta just below the level of the free edge of the right anterior cusp. It appears on the surface of the heart between the right atrial appendage and the conus arteriosus. Occupying the atrio-ventricular groove, it circles round the margo acutus as the posterior circumflex branch, crosses the posterior surface of the heart, and terminates by turning downwards on the posterior wall of the left ventricle.

The branches to the ventricles are as follows—

From the anterior portion:

1. A small twig curves over the conus arteriosus to anastomose with a branch from the left coronary.

2. One or more to the anterior wall of the right ventricle.

3. A ramus lateralis which descends the lateral wall of the right ventricle towards the apex of the heart. This may traverse the posterior wall of the right ventricle to reach the posterior interventricular sulcus.

From the posterior circumflex branch:

1. Several descending to the posterior wall of the right ventricle.

2. At the crux the ramus descendens posterior running in the posterior interventricular furrow for a varying distance.

3. One or more to the posterior wall of the left ventricle. The ramus descendens anterior and the ramus descendens posterior supply branches which pierce the interventricular septum.

From the main branches spread over the surface of the ventricles the finer muscular twigs enter at right angles. These rapidly form a fine arborization. The terminal filaments join freely to form a subendocardial network. It is around the muscle-fibres that the final capillary distribution takes place.

The subpericardial fat, chiefly found in the sulci, is supplied by tiny branches—arteriae telae adiposae—from the large vessels.

In rare cases a single coronary artery may be present, while in some they may be multiple. The latter arrangement arises usually when a vessel which commonly forms an anterior branch to the right ventricle has its origin from the aorta instead.

The Blood-supply to the Atria.

There is, with one exception, nothing constant in the distribution of the atrial blood-vessels. This is the ramus ostii cavae superioris. It is always present, it has no constant origin, but has a constant termination. It forms, or

helps to form, the ring anastomosis at the junction of the superior vena cava with the right atrium.

The general arrangement of these atrial vessels in shown in Fig. 2. Their names are indicative of their positions, e. g. ramus atrii sinistri posterior.

Fig. 3 illustrates the variations in the present series. With the exception of the ramus atrii dextri posterior, any of the atrial branches may form the ramus ostii cavae superioris. The latter commonly provides a branch which enters the interatrial septum, turns downwards, and takes part in the septal anastomosis.

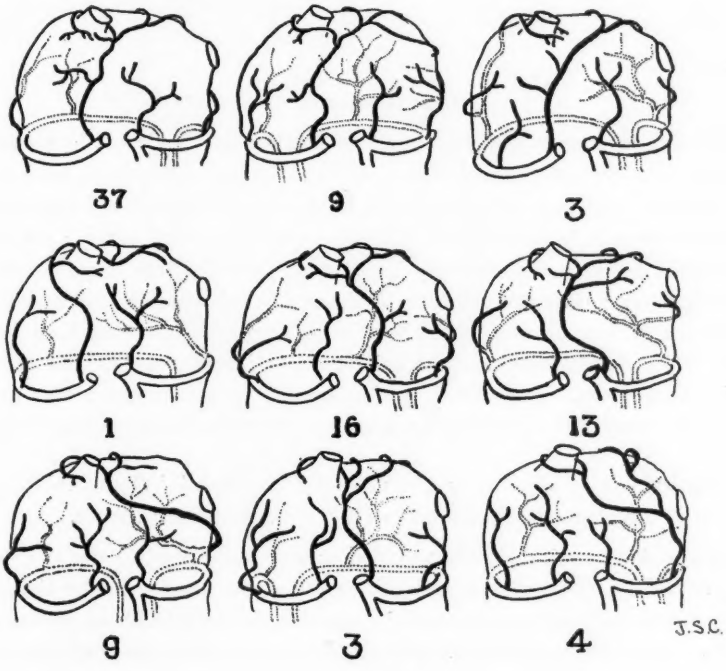


FIG. 3.

Of the origin of the ramus ostii cavae superioris, it occurred from the right coronary in 53 per cent. (60 per cent Gross); from the left coronary in 47 per cent. (40 per cent. Gross).

The Variations in the Ventricular Distribution of the Coronary Arteries.

On the anterior surface of the heart there is surprisingly little variation. Branches of the left coronary supply a varying amount of the lower segment of the right ventricle. The ramus descendens anterior is constant as a branch of the left coronary. The posterior surface presents a different picture and shows the commonest variation (Fig. 4). This concerns the size and distribution of the posterior circumflex arteries. The circumflex branch of the right

may be rudimentary, the left circumflex being large and extending beyond the crux to supply the posterior wall of the right ventricle.

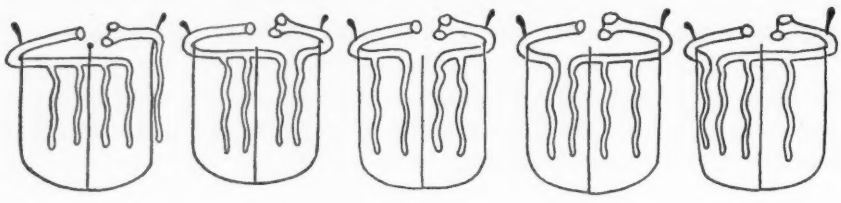


FIG. 4.

Anastomoses.

The literature on this much-debated subject has been reviewed by Gross, who states, from a study of normal hearts, that: (1) Anastomoses exist between the right and left coronary arteries both in capillary and precapillary distribution; (2) anastomoses exist between the branches of each coronary artery; (3) anastomoses exist between the coronary arteries and vessels from the adjacent and attached organs; (4) anastomoses in the heart are universal and abundant.

In the present series 1, 2, and 4 have been verified, 3 has not been investigated. The anastomoses show considerable variations, as do the coronary arteries themselves. They are best developed in the interventricular septum, around the apex, in the papillary muscles, and over the surface of the atria.

The Blood-vessels of the Interventricular and Interatrial Septa, with Special Reference to the Supply of the Neuromuscular Tissue.

Removal of portions of the ventricular wall made possible the stereoscopic study of the septal circulation and the supply of the neuromuscular tissue. In slicing the lateral portion of the right ventricle it is advisable to preserve part of the crista supraventricularis. Figs. 2 and 5 show the vessels of the septum, the former illustrating the general plan, the latter the detail of this circulation. Branches of the anterior descending ramus of the left coronary, spreading backwards, anastomose with the posterior descending ramus right coronary coming forwards.

(a) *The ramus septi fibrosi* arises at the crux from the posterior circumflex artery—occasionally from the ramus descendens posterior. Running anteriorly in the base of the interatrial septum, it penetrates the septum fibrosum, sends twigs to dip into the muscle of the interventricular septum and finally supplies the node of Tawara and bundle of His. In its course it gives off an ascending branch which anastomoses with the vessels of the atrial septum.

(b) *The ramus ventriculorum superior* has its origin in the upper portion of the ramus descendens posterior—occasionally from the circumflex artery. It supplies the upper portion of the interventricular septum.

(c) There are two branches of the ramus descendens anterior: 1. Close to

its origin a small twig is given off and curls downwards and backwards round the root of the aorta and crista supraventricularis. 2. The largest septal vessel, arising in the proximal inch, sends tributaries across the septum. One of these runs in the vestigial moderator band to reach the lateral wall of the right ventricle.

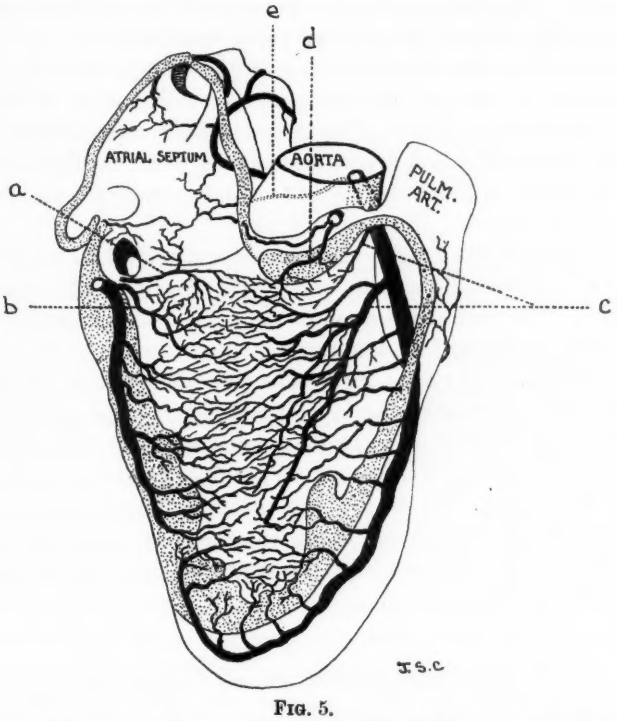


FIG. 5.

(d) *An artery*, of which no previous mention can be found, taking origin from the right coronary near its origin, occurs in 20 per cent. of the present series. It may conveniently be termed the ramus cristae supraventricularis. Leaving the under surface of the right coronary, the vessel runs downwards and backwards in the substance of the crista supraventricularis to reach the interventricular septum, where it anastomoses with the anterior septal branches of the left coronary and, in some instances, with the ramus septi fibrosi. Pl. 10' Fig. 6, is the radiogram of the upper portion of the septum from a case in which the artery was well developed.

(e) *Arteria anastomotica auricularis magna.* Kugel (2) describes this branch and found it arising from the left coronary in 66 per cent. of his series.

The Blood-supply of the Neuromuscular Tissue.

The sino-atrial node is supplied by the ramus ostii cavae superioris. It may, however, be supplied from one or other of the vessels forming the ring anastomosis encircling the superior vena cava.

The atrioventricular node and main bundle are supplied by a special artery, the ramus septi fibrosi. It is interesting to note that the vessel, as shown in Fig. 5, is seen to form seven distinct connexions. These are: (*a*) through its branch to the atrial septum, with a posterior atrial vessel, a descending branch of the ramus ostii cavae superioris, anterior atrial branches from the right and left coronaries; (b) in the interventricular septum, with branches from the right and left coronaries, and the ramus cristae supraventricularis.

The right limb of the bundle receives its blood-supply through the anterior septal branches of the left coronary. It is accompanied, in the vestigial moderator band, by an artery. The ramus cristae supraventricularis, when present, supplies blood from the right coronary—a point of clinical importance. The terminal twigs of the ramus septi fibrosi may supply the proximal portion of the right limb.

The left limb of the bundle spreads out as a thin sheet under the endocardium of the left side of the septum, receiving blood from the septal branches of both sides. The final arborization of the neuromuscular tissue is nourished by the profuse subendocardial anastomosis.

The variations in the coronary arteries have an important bearing on the septal circulation. The artery whose posterior circumflex reaches the crux will give origin to the septi fibrosi. In the present series it arose from the right coronary in 81 per cent. (Gross 92 per cent.); from the left coronary in 19 per cent. (Gross 8 per cent.). If both posterior circumflex arteries approach the crux, one may give off the ramus septi fibrosi and the other supply the lower septal vessels. In some cases the whole of the interventricular septum may be supplied by the left coronary artery.

Age Changes in the Coronary Circulation.

The vascular, more than any other system, progressively alters as age advances. The atrophic and degenerative changes of senility are due to vascular failure. Thinning of the capillary bed accompanied by insidious fibrous tissue replacement and the spread of arterio-sclerosis influence the physiological and pathological changes which occur.

The functional efficiency of the tissues depends on the condition of the blood-vessels. These progressive changes can be followed in radiograms of the coronary circulation taken at different periods of life and are well shown by Gross. Pl. 10, Figs. 7 and 8, are typical of hearts at birth and at the age of 45. In Fig. 7, the heart at birth, the blood-supply of the two ventricles is equal; the anatomical design alone distinguishes the sides. The arteries show no anastomoses in the interventricular septum. Arteriae telae adiposae are absent. During adolescence the right side is relatively decreasing in vascularity while the left increases, anastomoses in the interventricular septum are beginning to appear and arteriae telae adiposae are absent.

In Pl. 10, Fig. 8, from a patient aged 45, the blood-supply of the right side is

relatively diminished. Tortuosity of the smaller vessels is present. Anastomoses appear particularly in the interventricular septum. The arteriae telae adiposae have developed. In old age the vascular disparity of the two sides is now very marked, the right being relatively devoid of vessels while the left shows an increase. The vessels are very tortuous, especially the smaller. Anastomoses have increased and arteriae telae adiposae are better developed.

To interpret the radiograms of coronary disease correctly these age changes must be fully understood. It is sometimes difficult to determine whether or not a heart is pathological. The coronary circulation typical of a man aged 75 would, in a man of 50, be distinctly pathological, constituting premature senility.

Morbid Anatomy of the Coronary Circulation.

Stereoscopic radiography throws much light on the morbid anatomy of the coronary circulation, without which any clear conception of many aspects of cardiac disease is impossible.

Coronary disease is a precursor of myocardial insufficiency. With the diastolic blood-pressure fluctuates the volume of the coronary flow, a rise or fall in the former producing a similar result in the latter. The rate of the heart does not regulate this flow. Increased coronary flow required in response to effort is obtained by dilatation of vessels. This is a vagal reflex. Disease of the vessels which limits this reflex will, therefore, cause myocardial insufficiency.

The vessels may be affected either at their proximal extremities or in their ultimate ramifications. Amongst the earlier signs of coronary disease is a narrowing of the lumen of the small twigs of the coronary vessels. This gives these an appearance of having been nipped just at the point of leaving the parent vessel. If affected proximally the process is an arteritis or atheroma accompanying, as a rule, aortic atheroma. The finer vascular radicles, on the other hand, may be strangled, a fine fibrosis or degeneration of the cardiac muscle being the cause. This arises from a myocarditis, the primary factors more often being rheumatism or specific disease.

The present series throws into relief the relative frequency of coronary disease. Case after case which came to autopsy—many of them surgical, who had been operated on for conditions widely differing in character—revealed a greater or lesser degree of coronary trouble. To quote two illustrations alone: a woman was operated on for carcinoma of the breast. Within a week she came to autopsy and there was present a complete occlusion of the right coronary orifice by aortic atheroma, while the posterior wall of the heart showed a patchy fibrosis. A man, aged 60, underwent a radical operation for carcinoma of the rectum. Post-mortem three days later revealed a generalized sclerosis, more especially noticeable in the anterior descending branch of the left coronary, the outline of which was extremely irregular and showed marked nipping and great variations in the lumen. This was a case where at any moment complete occlusion might have occurred.

Coronary Occlusion.

Much attention in recent years has been focused on this subject and an extensive literature is in existence. This investigation has brought to light many interesting facts. Coronary occlusion was previously considered fatal. It is now clear that even occlusion in a main trunk of the coronary system is consistent with life. A syndrome of coronary occlusion is recognized. Repeated attacks of occlusion may occur. Of this the presence of healed infarcts is evidence. Occlusion of a coronary artery is usually followed by infarction.

It may be the result of arteritis or atheroma, thrombosis, embolism, or aortic disease.

Arteritis and atheroma. Usually atheroma of the aorta is present with coronary atheroma; the former may be slight and the latter very much predominate. There may be extreme stenosis of a large vessel. More often its branches are occluded at their origin, as occurs at a coronary orifice in aortic atheroma.

Thrombosis. A diseased vessel wall is an essential factor. The actual formation of the thrombus may be rapid or very gradual.

Embolism. This is the rarest cause; it is associated generally with ulcerative endocarditis. Occlusion, if it occurs in the earlier periods of life, is commonly embolic.

Aortic disease. The greater number of cases are luetic.

The importance of an occlusion is determined by its effect on the area supplied. The effect is determined by the following factors:

1. The vessel occluded.
   (*a*) Size and anatomical distribution.
   (*b*) Site of obstruction.
   (*c*) Rate of occlusion and anastomoses.
2. Condition of myocardium.
3. Blood-pressure.
4. State of the blood.

Dealing with these seriatim:

1. *The vessel occluded.*

(*a*) Size and anatomical distribution. A small muscular twig may be occluded, yet the anastomoses may be capable of supplying the area affected, or a tiny infarct may result. This, in time, is replaced by a fibrous scar. Only with multiple lesions of this type does the myocardial efficiency become seriously impaired.

The anterior descending branch of the left is fairly constant. The posterior mural supply is, however, variable. In consequence, an occlusion of the right coronary may in a few instances have no effect on the posterior surface of the heart, in some may affect the entire posterior wall, while in others only a postero-lateral strip of the right ventricle may be damaged.

(*b*) Site of obstruction. Reference to the diagrams (Figs. 3 and 4) will make quite clear the different sites and their probable results. Should a main branch be affected, the involvement of the branches will be governed by the site of the occlusion and the situation from which the radicle takes origin.

(*c*) Rate of occlusion and anastomoses. These, which develop with an ageing heart, are increasingly in evidence in some pathological hearts. Gradual obstruction, as when there is aortic atheroma or a gradual thrombosis, brings further increase in the anastomotic capacity.

When occlusion is complete the anastomotic network may have reached a stage which enables it wholly or partially to protect the section endangered. A sudden occlusion, as with an embolus, finds these compensating channels unprepared.

2. *State of the myocardium.* Any departure from the normal texture, such as an increase in fibrous tissue, will, by crushing out the smaller channels, interfere with the developing anastomoses.

3. *The blood-pressure.* This is important, as an increase will, by augmenting the flow in the compensatory vessels, tend to limit the extent of an infarction. A fall will have the reverse effect.

4. *The condition of the blood.* Any impoverishment in the blood itself will unfavourably load the balance in cases of coronary occlusion.

Infarction.

The gross macroscopic appearances are, in order, pallor of muscle, oedema, and colour gradually changing to grey. A line of demarcation forms and haemorrhages become evident, imparting a definite mottling to the area affected. Autodigestion commences, the infarct shrinks and is replaced by fibrous tissue.

The infarct is usually smaller than the area of distribution of the occluded vessel.

On the superficial surface it is unusual to see an infarction, the inner wall being commonly the part affected. The arteriae telae adiposae play an important role in protecting the superficial layer. The endocardium also, and a thin sheet of underlying muscle, may escape, due to subendocardial anastomoses and direct contact with the blood in the ventricle.

A heart included in the Gross series showed superficial infarction. He assumed that the subendocardial anastomoses were rich enough to supply the anaemic area. Apropos of this, Fig. 9 is interesting. The ramus lateralis (*a*) of the right coronary supplies the lateral wall of the right ventricle; (*b*) a large septal branch springing from the anterior descending branch of the left coronary passes backwards at the junction of the lateral wall of the right ventricle with the interventricular septum. Running under the moderator band, it turns upwards on the endocardial surface of the right ventricle, sending twigs outwards to meet the ramification of the ramus lateralis. In no other of this series has a branch of this magnitude been observed on the inner aspect of the heart. Had

the ramus lateralis or the right coronary been occluded suddenly, infarction might have been confined to the outer wall of the right ventricle.

Syphilis, as an etiological factor, is rarer. Of those coming into this group, aortic atheroma is the usual finding. Of cardiac infarction, 10 per cent., according to Parkinson and Bedford (3), are luetic, 17·5 per cent. according to Benson and Hunter (4).

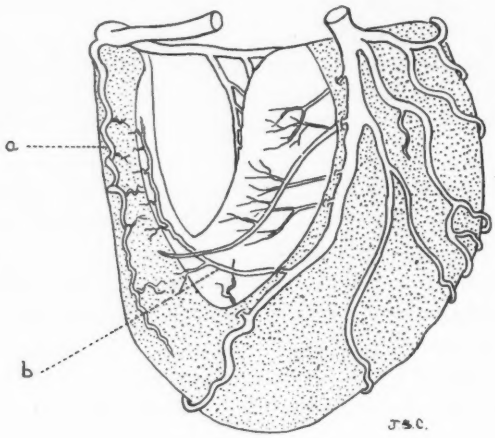


FIG. 9.

Complications of Infarction.

1. Intramural thrombosis.
2. Rupture.
3. Aneurism.

1. *Intramural thrombosis.* Owing to the shrinkage of the area of infarction depressions appear in the inner wall. In one a thrombus forms. From it emboli may be detached and swept to other organs.

2. *Rupture.* This is rare. In 200 cases of coronary occlusion reported by Benson and Hunter there were 14 cases of rupture. One of these cases perforated the interventricular septum. 50 per cent. were luetic. Of 83 cases reported by Parkinson and Bedford there were 5 cases of rupture.

The site of election of coronary thrombosis is the proximal couple of inches of the anterior descending branch of the left coronary. Where coronary sclerosis and atheroma were found in the present series the anterior descending branch of the left coronary suffered most. Even when the other vessels showed but little damage this artery was sometimes seriously involved. A thrombosis may become incomplete through shrinkage of the clot permitting some degree of flow to be re-established. Auto-digestion or shrinkage may also allow partial canalization to take place. To illustrate phases and types of coronary disease the following cases are recorded.

Case I. Male, aged 65 (Pl. 11, Fig. 10). *Cerebral thrombosis.*

(1) *Heart*: Fibrous myocarditis affecting chiefly the left ventricle.

(2) *Aorta*: Advanced atheroma partially obstructing right coronary orifice.

Radiogram.

Anatomical: Anterior and post-lateral walls of the right ventricle, right coronary supply; the rest of the heart, left coronary supply.

Age change: Relative preponderance of the left side less pronounced, owing to decrease in the finer vascular elements.

Left coronary: (*a*) Anterior descending branch.

(1) Contracted and irregular.

(2) Branches stenosed at origin.

(*b*) Posterior circumflex.

(1) Irregular.

(2) Posterior descending rami nipped.

(*c*) Ramus ostii cavae superioris stenosed at origin.

(*d*) Artery in moderator band anastomosing with ramus lateralis, right coronary.

Right coronary and branches not diseased to the same extent.

Anastomoses: Poorly developed, the finer vessels being strangled by fibrous tissue.

Case II. Male, aged 65 (Pl. 11, Fig. 11). Sudden death.

(1) *Heart*: Hypertrophied.

(2) *Aorta*: Sclerotic, atheromatous, calcareous.

(3) *Coronary arteries*: Orifices partially occluded. Main trunks hard, rigid, calcareous.

Radiogram.

Age change: Main stem not tortuous owing to rigidity. Otherwise typical.

(*a*) *Right coronary*: Thickened and calcareous.

(*b*) *Left coronary*: Thickened and calcareous.

(1) Main stem.

(2) Proximal two inches of anterior descending branch.

(3) Proximal half inch of circumflex branch.

The branches and finer ramifications of the coronary vessels are not affected.

Case III. Male, aged 57 (Pl. 12, Fig. 12).

Clinical diagnosis: Myocardial infarction. Died three weeks after admission. (Inversion of T Wave in leads II and III in electrocardiogram)

(1) *Heart*: Weight 18 ozs.

(2) *Aorta*: Atheroma.

(3) *Infarction*: Anterior wall left ventricle (large area), apex, lower anterior wall right ventricle (small area), interventricular septum (lower third).

(i) *The infarct.* Centre well organized.

(ii) *Wall of ventricle.* Marked thinning and apical hollowing.

(iii) *Intramural thrombosis.* Extensive.

Radiogram.

Anatomical:

1. *Right coronary*: Supplies anterior wall (except small apical sector), lateral wall, and lower third of posterior wall of the right ventricle.

2. *Left coronary*: Supplies remainder.

3. First ramus marginalis—the largest—rises at the bifurcation.

Thrombosis:

(*a*) of anterior descending branch for 2½ in. of its length. Its largest septal branch is given off proximally, where occlusion is incomplete.

(*b*) Bifurcation of largest ramus marginalis. At its bifurcation markedly stenosed.

(*c*) Post-circumflex branch, partial occlusion at its origin; otherwise not seriously diseased.

(*d*) Right coronary injected at two points. Between these thrombosis present.

Anastomoses: Beautifully developed.

1. Left ventricle, lower and posterior aspect: anterior descending ramus. left coronary. Rami marginales: posterior descending rami, circumflex branch (*e*).
2. Ramus lateralis, right coronary: anterior descending ramus, left coronary (*f*).
3. Interventricular septum very rich.
4. Right coronary: collateral vessels bridging thrombosed area. (These were sufficient to prevent infarction.)

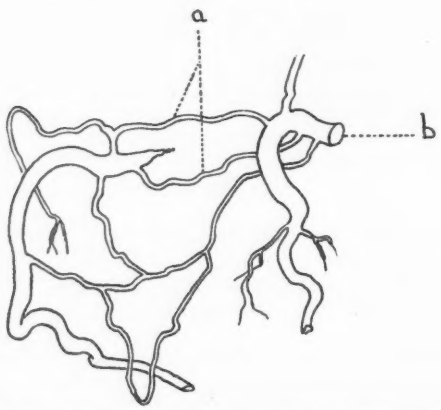


FIG. 13. (*a*) arteriae telae adiposae; (*b*) right coronary orifice.

Case IV. Female, aged 66 (Pl. 12, Fig. 14). Died twenty minutes after admission.

1. *Heart*: Hypertrophied.
2. *Aorta*: Atheroma—slight.
3. *Infarction*: Anterior wall of left ventricle, apex, and interventricular septum (lower third).
   (i) *The infarct*: centre, fibrous tissue.
   (ii) *Wall of ventricle*: inner and superficial aspects intact. Apical hollowing.
   (iii) Intramural thrombosis formed in depression.

Radiogram.

Anatomical:

1. Left coronary bifurcates almost at once.
2. First ramus marginalis—the largest—springs from circumflex branch of left coronary.

Thrombosis:

(*a*) of anterior descending branch of left about ¾ inch from its origin. Its largest septal branch is given off proximal to thrombus. No

muscular twigs are given off either the ill-defined anterior descending branch or its rami marginales. The muscular ramifications of the first ramus marginalis (a branch of the left circumflex) define the lateral border of the infarct (*b*).

Right coronary: Tortuous and irregular. Branches constricted at origin.

Anastomoses: (1) Rich in the interventricular septum.
(2) At the apex posteriorly.
(3) Posterior wall of left ventricle: a well-developed subendocardial network (chiefly in posterior papillary muscle).

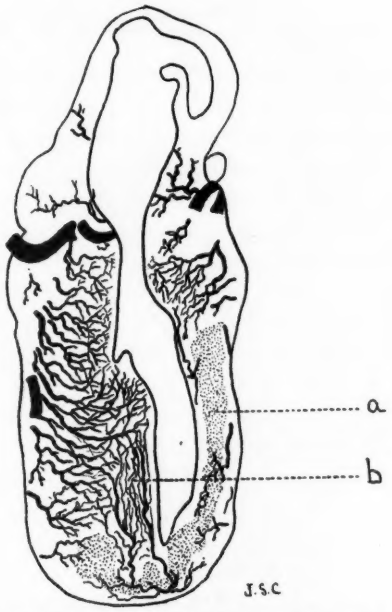


FIG. 15. Section from Pl. 12, Fig. 14. Line drawing of section through left ventricle: (*a*) infarct; (*b*) anastomotic network in posterior papillary muscle.

Case V. Female, aged 50 (Pl. 13, Fig. 16). Gangrene of right hand; thrombosis of radial artery.

Heart: Hypertrophied. Posterior wall, patchy fibrosis.

Aorta: Slight atheroma.

Radiogram: (Only left coronary injected).

Anatomical:

Right coronary: Supplies posterior walls of both ventricles.

Thrombosis: Right coronary.
(*a*) Main stem.
(*b*) Circumflex branch proximal to large descending ramus.

Remaining vessels are filled from left coronary, and, except for slight degree of nipping of radicles, not seriously diseased.

Left coronary: (*c*) Anterior descending branch. Slight stenosis. Otherwise healthy.

Anastomoses: Right coronary filled from left coronary to point of obstruction, chiefly through highly developed channels in interventricular septum. (Radiogram of septum, Pl. 16, Fig. 22.)

Case VI. Male, aged 52 (Fig. 17). Sudden death.
Heart: Hypertrophied, fibrous myocarditis.
Aorta: Atheroma.
Line drawing from stereo:
(*a*) *Thrombosis*: anterior descending branch left coronary.
(*b*) *Ramus cristae supraventricularis*: well developed. Is compensating supply to area which has suffered from the thrombosis of anterior descending branch of left coronary.

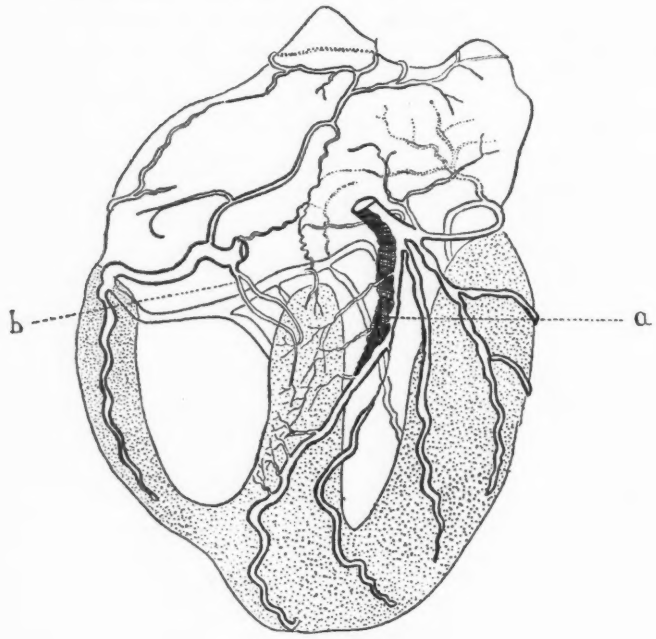


FIG. 17.

Sclerosis of the coronary arteries is relatively common. It is present in a varying degree in all old hearts, yet heart-block, bundle lesions, and other signs of interference with the conducting tissue of the heart are rare. Experimental and clinical evidence supports this. Smith (5), experimenting with dogs, was able to ligature main divisions of the coronary circulation without fatal results.

Electrocardiographic tracings taken at regular intervals for several weeks failed to show any lesion of the neuromuscular tissue.

In 100 cases of myocardial infarction, Parkinson and Bedford found abnormal rhythm only in 14: paroxysmal tachycardia, 2; paroxysmal fibrillation, 5; paroxysmal fibrillation plus tachycardia, 1; paroxysmal flutter, 3; paroxysmal flutter plus partial heart-block, 1; partial heart-block, 1; complete heart-block, 1.

The absence of bundle branch lesions and the very low incidence of heart-block are of interest. They record a case of complete heart-block which sub-

sequently disappeared. Wearn (6), in nineteen cases of coronary thrombosis, of which he had electrocardiographic records, found twelve with normal rhythm throughout, while two had a lesion of the conducting tissue. This, he states, seems remarkable in view of the nature and location of the lesion in the heart, for, in many instances, there was extreme damage to the septum. Hamman (7), reviewing the subject of coronary thrombosis, mentions the haphazard occurrence of the arrhythmias and wonders why one case should show these changes and another not.

Interference with the Blood-supply of the Neuromuscular Tissue.

An examination of the blood-vessels affords an explanation of the immunity possessed by the neuromuscular tissue in the majority of cases of coronary disease. General important anatomical features have to be considered. It has been shown that portions of the genetic system possess a specific blood-supply. These specialized arteries are: 1. To the sino-auricular node through the ramus ostii cavae superioris. 2. To the auriculo-ventricular node and bundle through the ramus septi fibrosi. 3. To the right branch of the bundle through the septal divisions of the anterior descending branch of the left coronary. With the exception of the septal divisions of the anterior descending branch of the left coronary these arteries may arise from either the right or left coronary.

Occlusion of two main types may be encountered, their results depending on, to a large extent, the anatomical arrangement of the vessels present.

1. *Obstruction in a main trunk.* Figs. 3 and 4 show the possibilities of an obstruction in a circumflex artery causing interference with the supply of the sino-auricular and auriculo-ventricular nodes.

With the exception of the anterior septal divisions of the left coronary, which invariably spring from the anterior descending limb of the left coronary, the remaining specialized arteries may arise either from the right or left coronary. The ramus ostii cavae superioris in 47 per cent. of cases of this series arose from the left coronary or its circumflex branch. Thrombosis of the right coronary or its circumflex branch, will not, in these instances, influence the supply of the sino-auricular node. That of the left coronary, on the other hand, may or may not, depending on its site—whether proximal or distal to the origin of the ramus ostii cavae superioris. Should the right coronary or its circumflex branch be thrombosed, in 19 per cent. of hearts the auriculo-ventricular node and bundle will be unaffected (Fig. 4).

2. *Obstruction in a specialized artery.* Sino-auricular node: ramus ostii cavae superioris. Infrequently this is not the direct supply of the node, some other vessels entering the ring anastomosis fulfilling this function.

Auriculo-ventricular node and bundle: ramus septi fibrosi—the constant vessel of the node and bundle—typically possesses an ascending branch to the interatrial septum which may determine the lesion following obstruction to the parent vessel according to its site (Fig. 5).

There is more likelihood of an obstruction of the ramus septi fibrosi causing lowered activity of the auriculo-ventricular node and bundle if the atrial branch is absent, or the obstruction distal to its origin.

The right branch of the bundle. Anterior septal divisions of anterior descending branch of left coronary. The free anastomosis between these and those of the opposite side protects this bundle branch. A ramus cristae supraventricularis, when present, provides an additional protection from the right coronary.

The left branch of the bundle. Owing to its diffuse blood-supply and structure this suffers less from vascular changes.

The neuromuscular tissue owes much to the richness and arrangement of its anastomotic network—a network the capacity of which becomes greater as the years advance. Gradual obstruction produces a similar result. Special emphasis is laid on the collaterals reaching the ramus septi fibrosi along the atrial septum (Fig. 5).

Two cases of Stokes-Adams syndrome are recorded by Géraudel (8), who, by serial section, demonstrated stenosis of the ramus septi fibrosi. Both had an intact auriculo-ventricular node and bundle. He propounds a theory—'L'hypothèse des cardionecteurs à régime circulatoire variable'—(cardionecteurs—atrial and ventricular connecting tissues) that alterations in the blood current to the sino-auricular node and auriculo-ventricular node caused disturbances in rhythm and rate of the heart-beat. That the activity of a node varies directly with the volume of blood reaching it, increasing with a larger volume, decreasing with a reduced one. That stenosis of a specific artery (e.g. ramus septi fibrosi) causes asynchronism of auricles and ventricles.

Sclerosis in the coronary system is common, in which the ramus septi fibrosi has no special immunity, but, with this, rhythmic disturbance is seldom met, while heart-block and bundle lesions are still less frequent. The theory fails to appreciate that anastomoses may counteract the evil effects of stenosis.

A survey of the present series of cases of coronary thrombosis and sclerosis suggests that stenosis of the specific arteries will not usually interfere with the activity of the neuromuscular tissue. Even complete occlusion of these vessels may fail to produce heart-block owing to the anastomic compensatory channels.

In the majority of cases of advanced coronary disease electrocardiographic and clinical records were not obtained, due either to the grave condition of the patients when first seen, to their decease before admission to hospital, or to their not having been diagnosed prior to autopsy. Two, in which records were obtained, are of special interest. One showed partial heart-block, the other a right bundle branch lesion. These, with other cases illustrating points of clinical interest in connexion with the septum, follow.

Case VII. Male, aged 67 (Pl. 13, Fig. 18). Partial heart-block.
Heart: Greatly hypertrophied. Weight 28 oz.
Aorta: Atheromatous.
Aortic cusps: Sclerosed and atheromatous.
Radiogram of septum:
(*a*) Ramus septi fibrosi, stenosed at point indicated by arrow. It is to be

particularly noted that the stenosis is distal to the origin of a large branch anastomosing with vessels in the arterial septum.

(*b*) Anastomosis between a terminal twig of (*a*) and branch of the ramus ventriculorum superior.

(*c*) Ramus descendens anterior, left coronary; narrowed and irregular. Its large septal branch is constricted at its origin.

Stenosis, distal to its atrial branch, of the artery to the auriculo-ventricular node and bundle in a case of partial heart-block.

Case VIII. Female, aged 50 (Pl. 14, Fig. 19). Right bundle branch lesion.

Heart: Hypertrophied.

Aorta: Thickened and atheromatous.

Aortic cusps: Sclerosed, especially the posterior.

Myocardium: Fine fibrous myocarditis. The right branch of the auriculo-ventricular bundle, at the junction of the septum membranaceum and muscular septum, was embedded in dense fibrous tissue. The septum membranaceum was thickened and contracted. The fibrous tissue appeared to spread downwards from the root of the aorta and posterior aortic cusp.

Radiogram of heart showed:

The outstanding feature is loss of the finer vascular elements without any great interference with the larger arteries. The anterior descending branch of the left coronary—so often the seat of disease—appears healthy. The myocardial condition has probably been the result of an infectiv myocarditis rather than coronary disease.

Radiogram of septum:

Absence of fine vessels.

(*a*) Thickened posterior aortic cusp.

(*b*) Ramus septi fibrosi. Its atrial branch anastomoses with a posterior atrial artery.

(*c*) Narrowing of artery in the moderator band.

(*d*) Anastomotic connexion between anterior and posterior descending branches of left and right coronaries.

Site of fibrosis involving the right limb of the bundle is shown by the arrow.

Fig. 20. *Radiogram of septum of heart* (Pl. 14, Fig. 15).

Advanced generalized coronary sclerosis. Electrocardiogram did not reveal interference with the genetic system.

With the exception of one small twig, the left coronary supplies the interventricular septum.

(*a*) Ramus septi fibrosi, stenosed at point of origin, possesses a well-developed branch, communicating with a profuse network of vessels in the interatrial septum.

(*b*) Narrowed and irregular anterior and posterior descending rami. The septal branches are nipped as they leave their parent stems.

(*c*) Large anterior septal division stenosed at its origin, anastomoses with:

(*d*) Ramus cristae supraventricularis, the twig from the right coronary.

Stenosis of arteries to the auriculo-ventricular node and bundle without clinical evidence of a neuromuscular lesion.

Stenosis of the artery to the auriculo-ventricular node and bundle proximal to the branch to the interatrial septum.

Pl. 15, Fig. 21. *Radiogram of septum of heart* (Fig. 11).

(*a*) Ramus septi fibrosi sends a delicate twig to the interatrial septum.

(*b*) Anterior descending branch of the left coronary with thickened

calcareous wall. Two septal branches arise from the diseased portion, and, especially the first, have partially occluded orifices.

(*c*) Ramus cristae supraventricularis ; right coronary anastomosing with the ramus septi fibrosi and the first anterior septal branch.

(Extensive antero-posterior anastomoses are seen.)

The presence of the ramus cristae supraventricularis is important as it supplies blood to an impoverished area.

Pl. 16, Fig. 22. *Radiogram of septum of heart* (Fig. 16).

Complete occlusion of the right coronary by thrombosis which extended one inch along the circumflex branch. The left coronary alone has been injected.

(*a*) Posterior descending branch, right coronary.

(*b*) Anterior descending branch, left coronary.

The vessels of the septum from the right coronary have been filled through wide anastomotic channels from the left coronary.

The terminal filaments of the ramus septi fibrosi are not shown.

(*c*) A specially well-developed twig from the left coronary.

Pl. 16, Fig. 23. *Radiogram of septum of heart.*

Right coronary orifice completely occluded by atheroma.

Left coronary alone injected.

Right coronary :

(*a*) Posterior descending branch.

(*b*) Ramus septi fibrosi, filled from the left coronary through a network of fine twigs.

Left coronary :

(*c*) Anterior descending branch.

Summary.

1. From a study of 100 hearts it may be said that stereoscopic radiography is of much value in demonstrating the cardiac lesions which come to autopsy and can do much to give a clearer conception of the course of those lesions which have a fatal termination.

2. Variations in the anatomical distribution of the coronary vessels are very frequent. They have a definite bearing on the clinical aspects of coronary disease.

3. The age changes and anastomoses described by Gross have been verified.

4. Anastomoses fulfil a function in preserving the cardiac muscle, which increases in importance in cases of coronary disease.

5. The neuromuscular tissue is specially safeguarded by many alternative channels of supply. In two of the series even stenosis of the specific artery to the node and bundle failed to give any electrocardiographic evidence of a lesion.

6. Coronary disease is relatively common though often quite unsuspected.

7. Within very considerable limits the heart is able to adapt itself to even marked alterations in the lumen of its vessels or the sources of its supply, provided only the lesion is not too sudden in onset or too extensive in degree.

My best thanks are due to the Honorary Staff of the Royal Victoria Hospital for the material put at my disposal ; to Mr. Leman and Miss Baird of

the Radiological Department, for their unfailing courtesy and assistance; and to the Laboratory Staff for their help in preparing the injected specimens.

In particular I wish to thank Dr. L. N. Ross for his generous help in the preparation of this article.

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FIG. 6

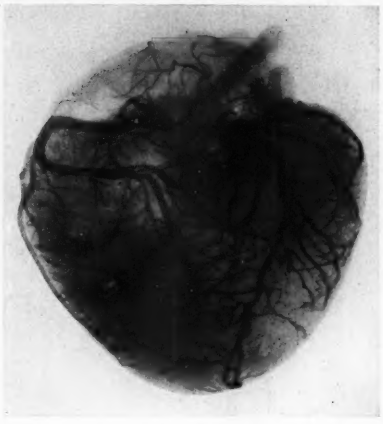


FIG. 7

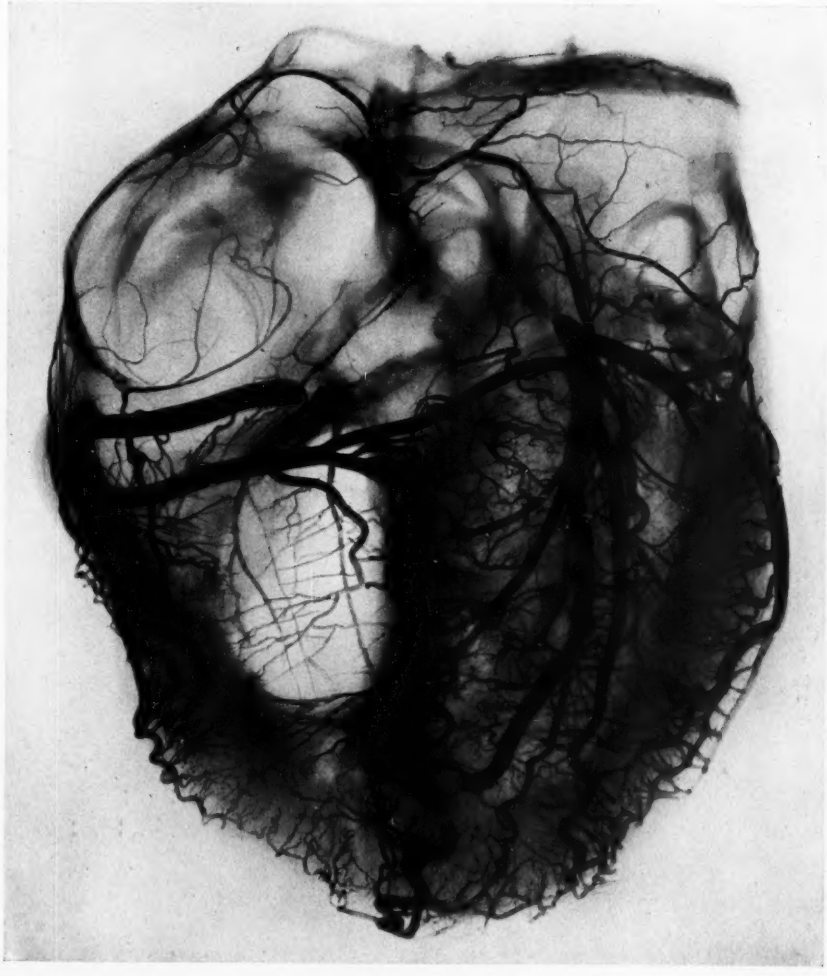


FIG. 8

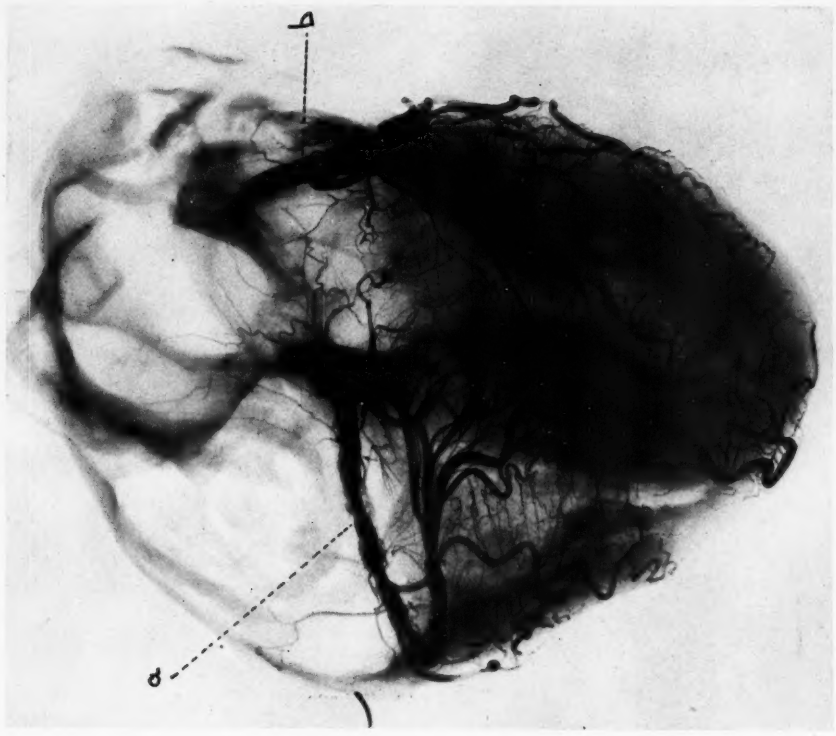


FIG. 11

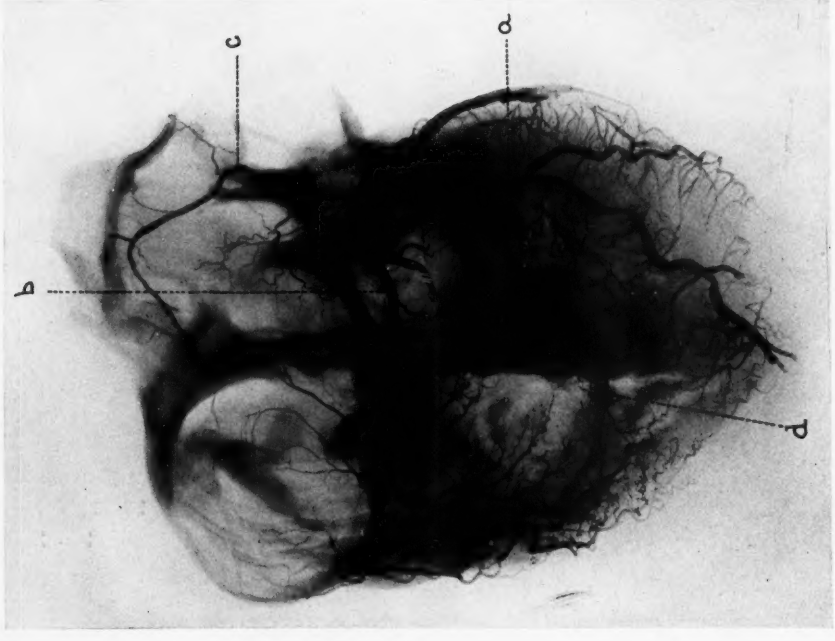


FIG. 10

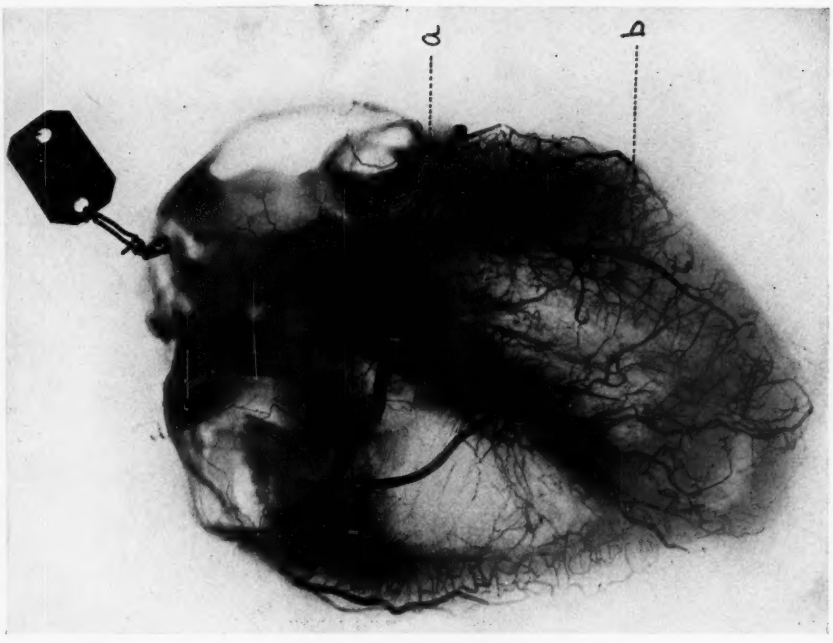


FIG. 14

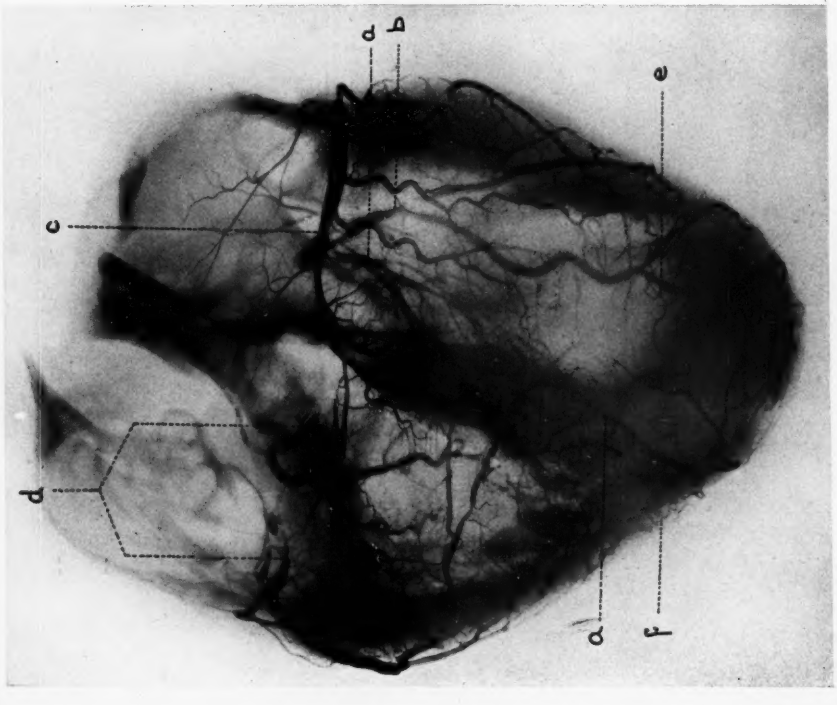


FIG. 12

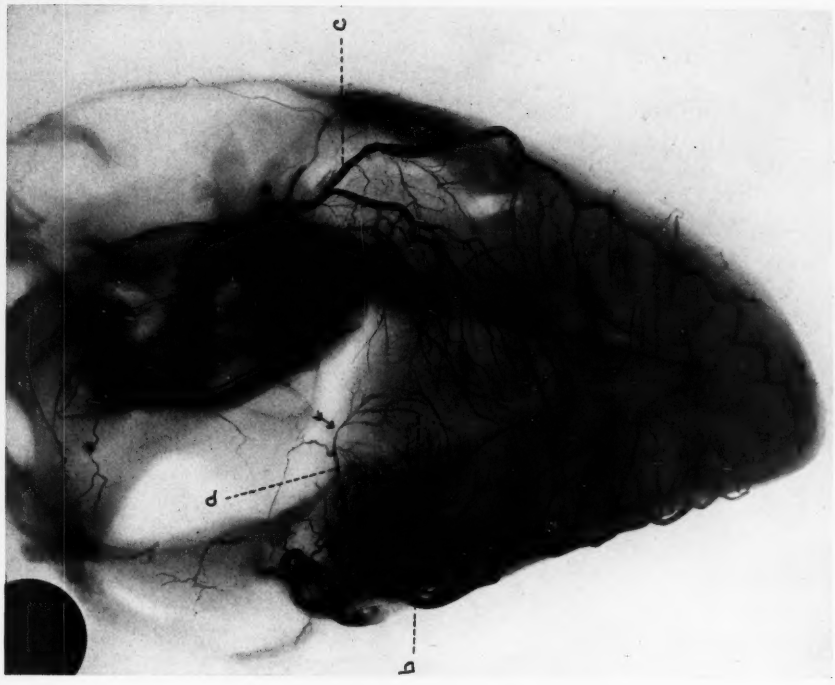


FIG. 18

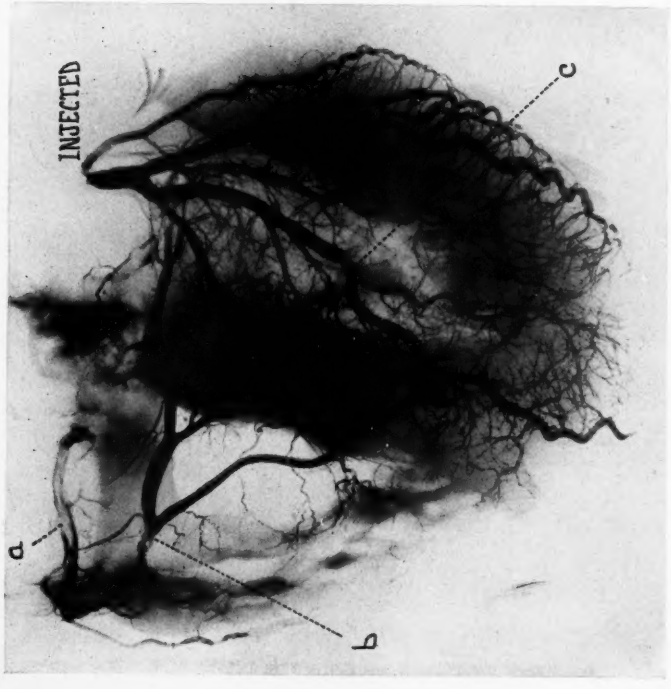


FIG. 16

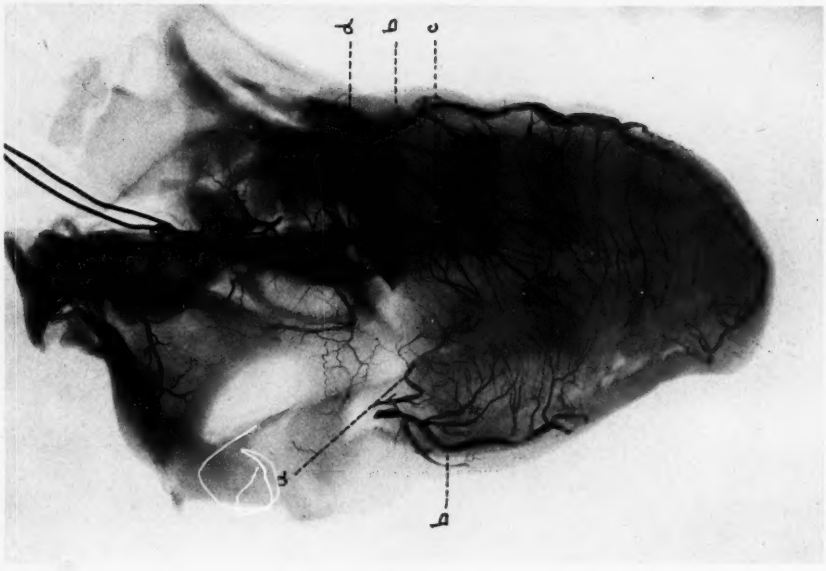


FIG. 20

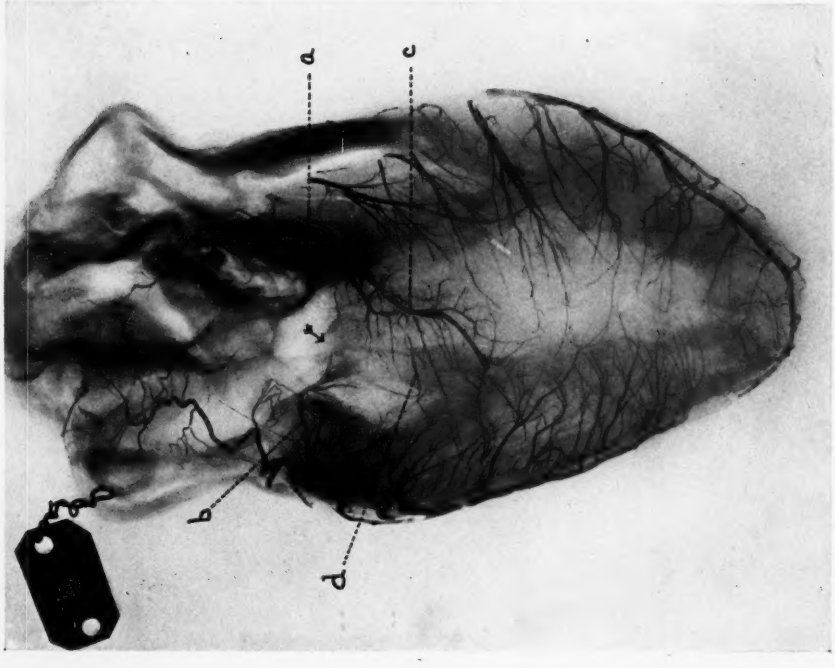


FIG. 19

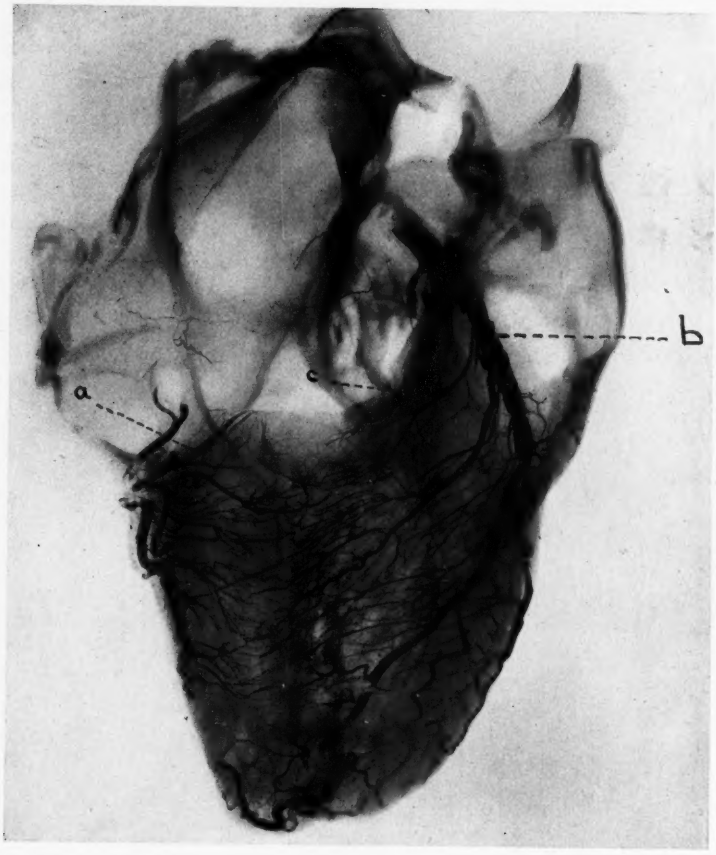


FIG. 21

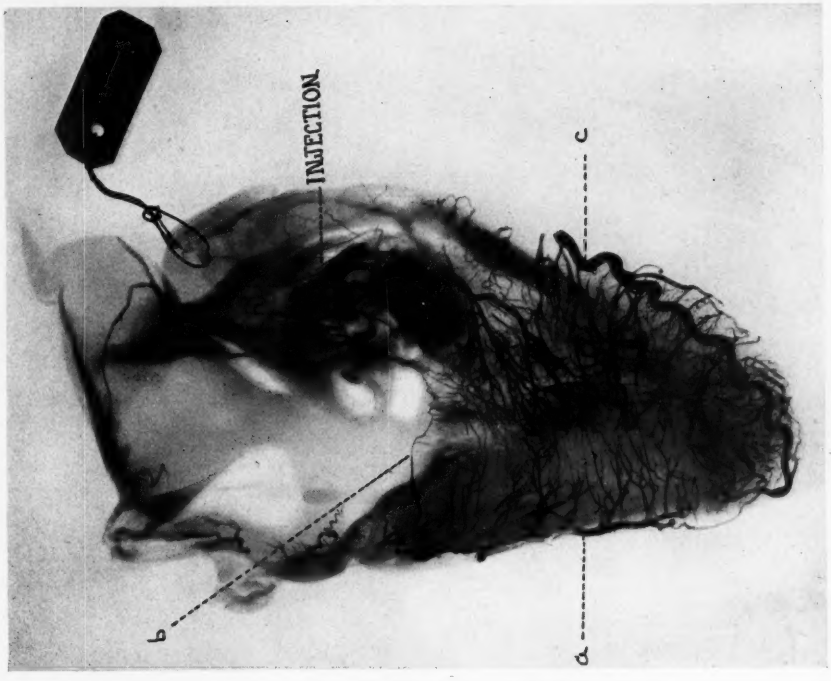


FIG. 23

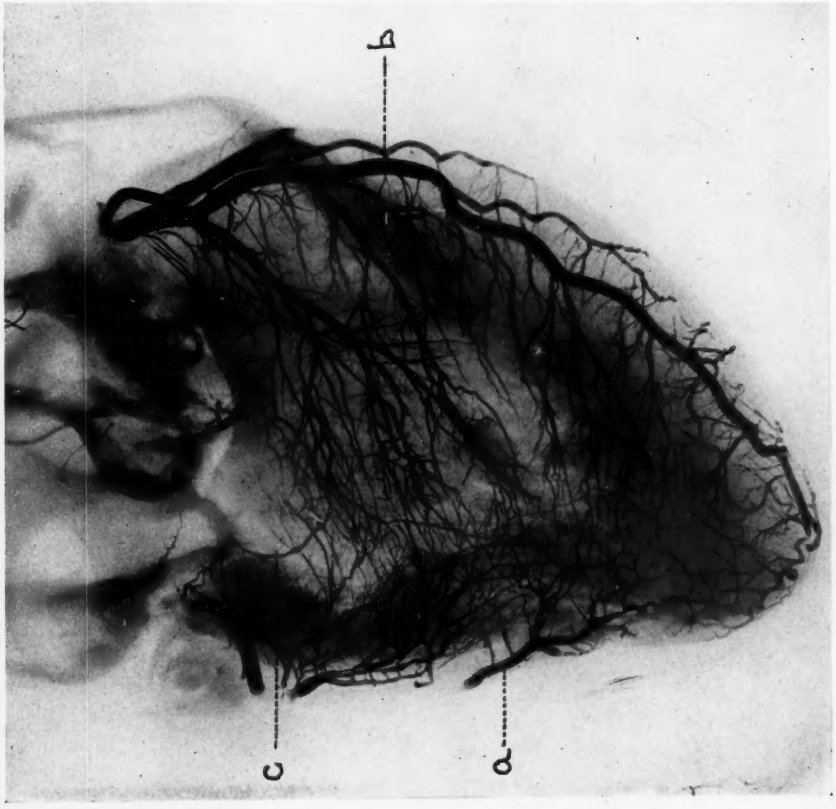


FIG. 22



THE TREATMENT OF CERTAIN FORMS OF INFANTILE ATROPHY WITH ATMOSPHERES ENRICHED BY OXYGEN AND CARBON DIOXIDE[1]

By EDITH F. W. McCREA and H. S. RAPER

(From the Manchester Babies' Hospital and the Physiology Department, University of Manchester)

In 1926 Botwood, Raper, and Willock (1) published a preliminary account of the use of atmospheres enriched with oxygen and carbon dioxide in the treatment of a certain type of infantile atrophy. The results obtained up to that time were definitely promising, and since then the investigation has been continued and extended. We are now able, therefore, to describe the results obtained in twenty-one cases.

The term atrophy may be used to describe those infants who obstinately refuse to gain weight and thrive, without any apparent cause. A certain number of these infants suffer from endocrine or vitamin deficiency, and will respond to appropriate treatment. Others may be classed as starvation atrophies, and dietetic measures usually succeed with these, while in some cases the condition may result from an initial dyspepsia—the dyspeptic atrophies; dyspepsia, however, is not often associated with the atrophic state, and when present it is frequently the result, rather than the cause, of the condition. There remains, however, a group of infants who fail to respond to any of the above measures, and it is with these that we are concerned.

The atrophic infant, if untreated, will probably live for some months, taking feeds well and showing no gross symptoms of disease beyond a persistent refusal to gain weight and thrive like a normal infant. An intercurrent disease, such as pneumonia, frequently develops, to which the infant succumbs with extreme rapidity, or the state of metabolic equilibrium, for no apparent reason, becomes upset, weight is rapidly lost, and death occurs with startling suddenness.

Necropsies in these infants often, if not invariably, fail to reveal any definite organic lesions. This suggests the existence of some fundamental physiological disability. In our preliminary paper the view was put forward that this was possibly an anoxaemia due perhaps not so much to deficient pulmonary function, though the occasional bluish tinge of these infants indicates that possibility, but rather to a localized tissue anoxaemia such as may occur in shock from stagnation of the blood-flow in certain areas. It was suggested that a capillary

[1] Received October 1, 1928.

stasis, in the small intestine for instance, leading to deficient absorption might account for some of the phenomena shown by the cases with which we are dealing. There is no need to labour the point that a condition of this kind would seriously impair the physiological functions of an animal, and it therefore seemed possible that such a disturbance might be a cause of certain types of infantile atrophy. For this reason treatment in the first instance by the use of atmospheres enriched with oxygen and carbon dioxide was carried out, with, it must be admitted, no great hopes of success. But the early cases responded so well to this method that it seemed justifiable to consider their original condition as due to anoxaemia. In a group of cases treated later, almost equal success has been obtained by the use of air enriched with carbon dioxide alone, so that the earlier results must be ascribed to a combination of the effects of oxygen and carbon dioxide. The success with carbon dioxide alone does not invalidate our first hypothesis that a certain degree of oxygen lack may be a cause of infantile atrophy. It does, however, show that the results of the treatment are not due solely to the breathing of an oxygen-rich atmosphere, but to other factors as well. The increased carbon dioxide of the air breathed will promote deeper breathing and will tend to improve the oxygenation of the blood, the venous return to the heart, and the arterial blood-pressure, thus markedly aiding the circulation-rate.

An examination of the venous carbon dioxide pressure in several of the cases by the Henderson and Prince method (2) showed that it was greater after the period of treatment in the cot than previously. This has been taken to mean that the carbon dioxide capacity of the blood has increased. A quantitative examination of the urine has also shown that, as an accompaniment to this change, there is a diminution of the percentage of the total nitrogen of the urine, which is excreted as ammonia (ammonia coefficient). The association of the increased carbon dioxide capacity of the blood with a lowering of the ammonia coefficient, as a result of the treatment, indicates that initially a certain degree of acidaemia existed.

These facts indicate that it is not possible to state that the improvement resulted because of any one of them. It is more likely that all contributed to the attainment of a more normal physiological condition of the organism as a whole.

Methods and Results.

The investigation has been carried out almost entirely at the Manchester Babies' Hospital, and we are indebted to Dr. Catherine Chisholm for the facilities offered to us there.

The infants selected for the experimental work have been those who obstinately refused to gain weight and respond to prolonged dietetic and therapeutic measures. Every effort was made to ensure accuracy in the careful selection of cases, by excluding those with any symptoms which would account

for the atrophy, and to rule out any possible factor of improvement other than the treatment in the closed cot during the experimental period.

The cot used consists of an airtight box (29 in. × 29 in. × 18 in.) with a movable glass lid (Figs. 1 and 2); an inlet pipe admits oxygen at a known

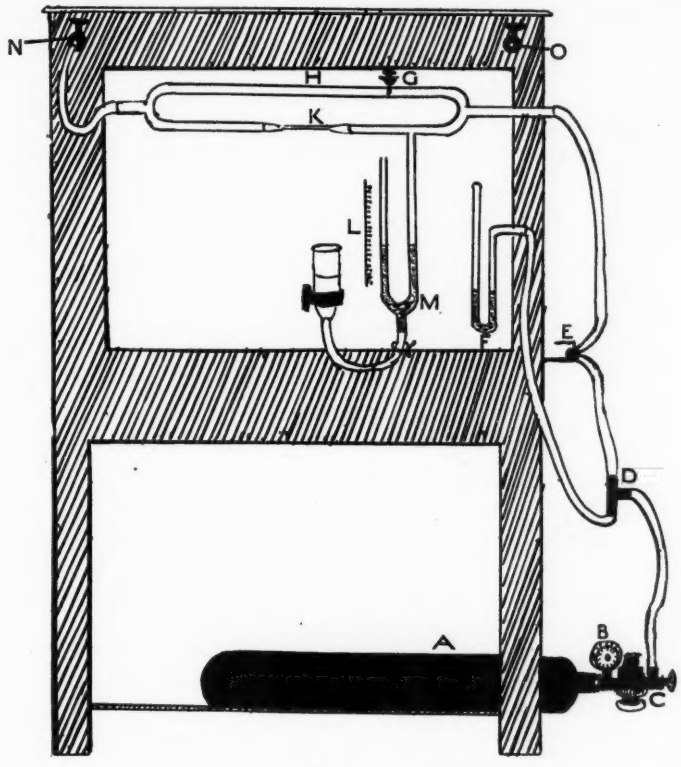


FIG. 1.

A. Oxygen cylinder.
B. Pressure gauge.
C. Reducing valve.
D. Glass T-piece.
E. Fine adjustment tap.
F. Mercury manometer (closed).
G. Tap.
H. Wide-bore brass tube.
K. Capillary glass tube.
L. Scale.
M. Water manometer.
N. Inlet pipe to cot.
O. Sample tube from cot.

rate, and a second pipe permits of samples of air being drawn off when desired for purposes of analysis. A small electric fan inside the cot serves to keep the air in motion, and a thermometer records the temperature. The infant lies on a hammock inside the cot, and the lid is clamped down. Oxygen is admitted from a cylinder, provided with a reducing valve and pressure gauge, and passes through a modified Pitot's tube, whereby, after a preliminary standardization, the rate of flow necessary to produce the required concentration of oxygen can be ascertained. If oxygen enrichment is desired then the oxygen is at first admitted rapidly until the cot atmosphere contains approximately 40 per cent.

oxygen; the inflow is then reduced so as to maintain the oxygen content at about this level. No effort is made to remove the carbon dioxide expired by the child, and analyses have shown that at the end of a two-hour period this rises to between 2 per cent. and 3 per cent. The infant remains completely enclosed in the cot for periods of two hours at a time, and is then removed for purposes of feeding and other nursing requirements.

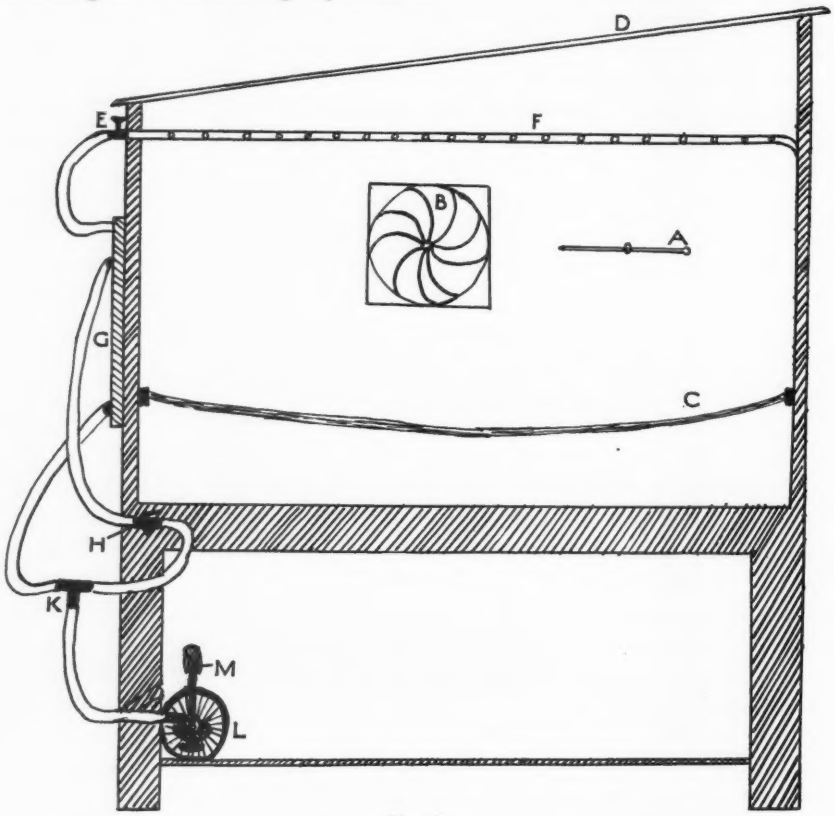


FIG. 2.

A. Thermometer.
B. Fan.
C. Hammock.
D. Adjustable glass lid.
E. Tap.
F. Perforated oxygen inflow pipe.
G. Manometer board.
H. Fine adjustment tap.
K. Glass T-piece.
L. Oxygen cylinder and reducing valve.
M. Pressure gauge and tap.

When after some months of unavailing dietetic and medicinal treatment a case was selected as suitable for the present investigation, no change was made in the type of diet for some two or three weeks prior to the child being actually placed in the cot, and all drugs and other treatment were discontinued. The cot treatment was then commenced and lasted for varying periods of three to six weeks; the actual periods of enclosure in the cot were only carried out during the daytime, and amounted to eight or ten hours in two-hourly periods;

during the remainder of the twenty-four hours the infant remained in the same cot, but the lid was not closed down. Increases in the quantity of the child's food were made when necessary, but no change was permitted in the type of diet during the experimental period, or for the preceding or succeeding two or three weeks, nor was any other coincident treatment allowed.

In the earlier cases, nine in number, the infants were exposed to atmospheres containing approximately 40 per. cent. oxygen and their expired carbon dioxide was allowed to accumulate, usually reaching from 2 per cent. to 3 per cent. Later, in order to ascertain the relative benefits due to these two gases, a group of eight cases were first given three weeks' treatment in the cot with the oxygen kept at approximately the normal atmospheric level, and this was followed by three weeks' treatment with the oxygen enriched to 40 per cent. In both instances the carbon dioxide produced by the infant was allowed to accumulate during the two-hourly periods. The comparative rates of progress were then carefully noted. A third group of four cases were subjected to four or five weeks' treatment with increased carbon dioxide alone, without any oxygen enrichment.

In seven of the later cases, analyses of twenty-four hour specimens of urine were made before, during, and after treatment. The titration acidity to phenol phthalein and alkalinity to methyl orange were estimated, also the ammonia content, total nitrogen, and pH, and the ammonia coefficient was calculated. Some difficulty was experienced in collecting twenty-four specimens from such small infants, but an apparatus was devised which gave good results though occasionally small quantities of urine escaped.

The apparatus used (Fig. 3) consisted of a small oval cup of firm rubber, with a thickened rim; in a male infant the whole scrotum and penis was encircled by the cup, in a female, the vulva, and it was secured in position by tapes round the waist and groins. Distally the cup tapered to a glass tube and this was connected by rubber tubing to a bottle, in which the urine was collected under a thin layer of toluene. A little skill in the adjustment of the apparatus enabled the urine to be collected without faecal contamination; the infants were kept in a prone position during the taking of each urinary specimen, and did not as a rule resent the process to any great extent. At first there was some degree of irritation of the vulva or scrotum, presumably caused by the action of the urine on the rubber of the apparatus. This difficulty was obviated at first by coating the rubber in contact with the skin by a thick layer of collodion, and later the apparatus was constructed of differently prepared rubber, which did not seem to cause any irritation at all.

It seemed desirable to obtain some information as to the combining capacity of the blood for carbon dioxide, but the infants were so small that arterial puncture was out of the question, and it was also impossible to collect samples of alveolar air by the Haldane-Priestley method. We therefore had recourse to the method of Henderson and Prince (2), which gives approximately the percentage of carbon dioxide in equilibrium with the mixed venous blood. This

determination was made on three of the cases. The apparatus used consisted of a rubber and metal face-piece to which was attached a thin rubber bag, with a capacity of about 250 c.c. A tap was inserted between the bag and face-piece and a small side-tube, with tap, permitted a sample of the contents of the bag to be drawn off for analysis when desired. The bag was filled with air of a known low carbon dioxide percentage, and the infant made to breathe in and out of the

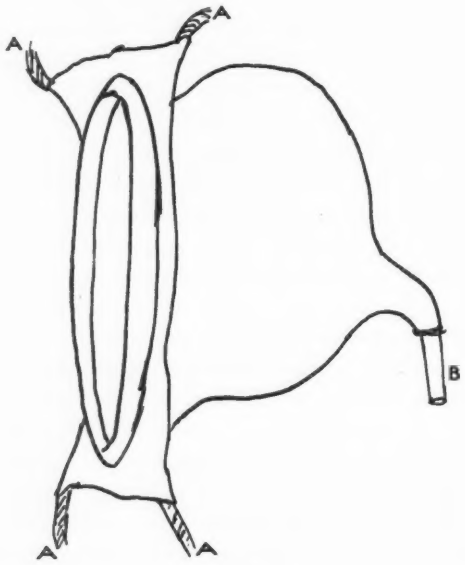


FIG. 3.

A. Straps. B. Glass connexion to collecting bottle.

bag for periods of ten to twelve seconds; the tap between bag and face-piece was then closed and the carbon dioxide content of the air in the bag estimated; the experiment was then repeated until the carbon dioxide content reached equilibrium. A similar series of observations was also made in which the initial carbon dioxide percentage in the bag was high; graphs of the results were plotted and the percentage of carbon dioxide in equilibrium with the venous blood was thus obtained. Control estimations were carried out for comparison on selected, apparently healthy infants of similar ages to those treated in the cot.

The following brief descriptions of typical cot cases and the effects of treatment will serve to indicate the results obtained.

Case 18. W. B., a male infant of 7 weeks, was admitted with a history of persistent failure to thrive; he was a thin but big-boned child, weighing 7 lb. 8 oz.; his appetite was poor and he was extremely fretful. Dietetic and medicinal treatment was carried out for nearly five months, at the end of which period the infant had lost 1 lb. in weight, for no very obvious cause. At this stage the child was undoubtedly going down hill rapidly. He was put into the cot, without oxygen enrichment (the diet having been unchanged in type for

the previous ten days), and after a brief stationary period he commenced to gain weight and to improve markedly. During six weeks in the cot 19 oz. were added, and a further gain of 17 oz. before discharge a month later (see Weight Chart I). Owing to the child's rapidly deteriorating condition, only one urine analysis could be carried out prior to cot treatment; the ammonia coefficient was then 7·4, after treatment the average was 6·1.

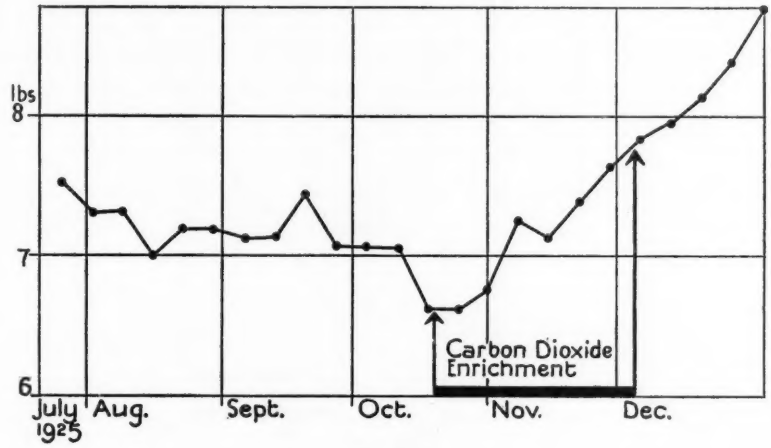


CHART I.

Case 20. C. B., a female infant, aged 3 weeks; on admission she was a small but quite well-nourished child, weighing 7 lb. 13 oz. She had no dyspepsia or other apparent disease, but after three and a half months of dietetic and therapeutic treatment she had only gained 6 oz. After five and a half weeks in the cot, without oxygen enrichment, she had gained 26 oz. and a further 35 oz. were added during the ensuing seven weeks before discharge (see Weight Chart II). The infant was then fat and healthy. The ammonia coefficient prior to cot treatment averaged 7·4, after treatment 3·6. 'Alveolar' carbon dioxide before treatment, 3·7–4·4 per cent.; after the cot treatment, 4·9–5·5 per cent.

Case 19. D. O., a female infant, aged 3½ months, weighed 8 lb. 5 oz. on admission to hospital; she was small but moderately well nourished and had no dyspepsia or other apparent disease. Four months after admission she had been subjected to various measures of treatment, dietetic and otherwise, and at this period only weighed 7 lb. 14 oz. She was put into the cot, without oxygen enrichment, and after seven weeks on an unchanged type of diet she had gained 27 oz.; a further 35 oz. were added before discharge five weeks later (see Weight Chart III). Ammonia coefficient before treatment, 12·3; after four weeks in the cot, 9·8; after completion of treatment, 4·1. 'Alveolar' carbon dioxide before treatment, 4·1–4·8 per cent.; after treatment, over 5·2 per cent.

Case 6. K. B., a male infant, aged 2½ months, was admitted to hospital with a history of 'wasting'. He then weighed 6 lb. 8 oz. and proved to be a thin, miserable child. No definite organic disease could, however, be found. For six weeks dietetic and therapeutic measures were carried out, but only 2 oz. were gained during this time. The type of feed having been unaltered for two weeks, the infant was placed in the cot and for three weeks received both increased oxygen and carbon dioxide. While in the cot, 10 oz.

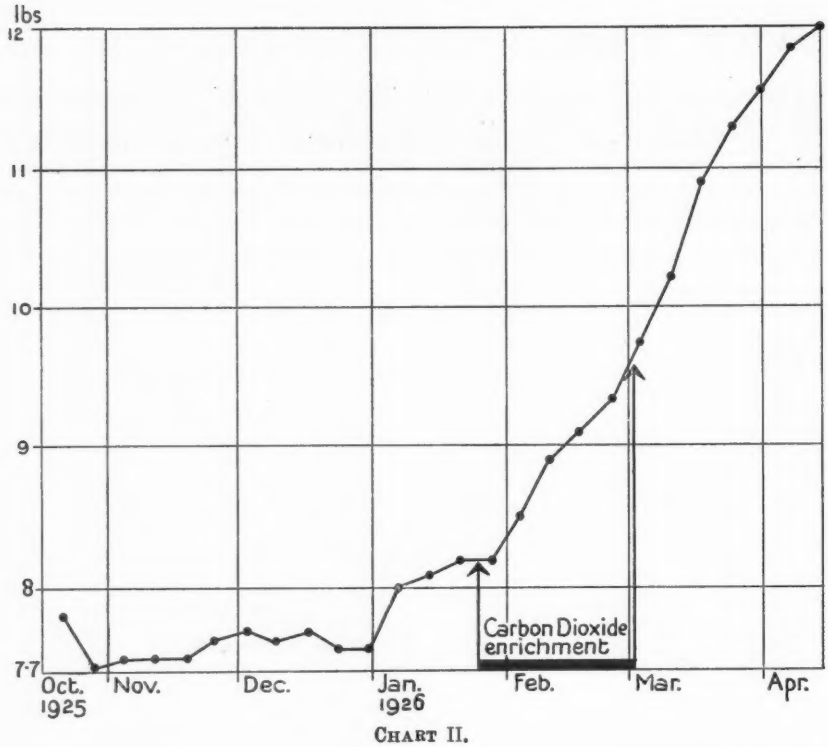


CHART II.

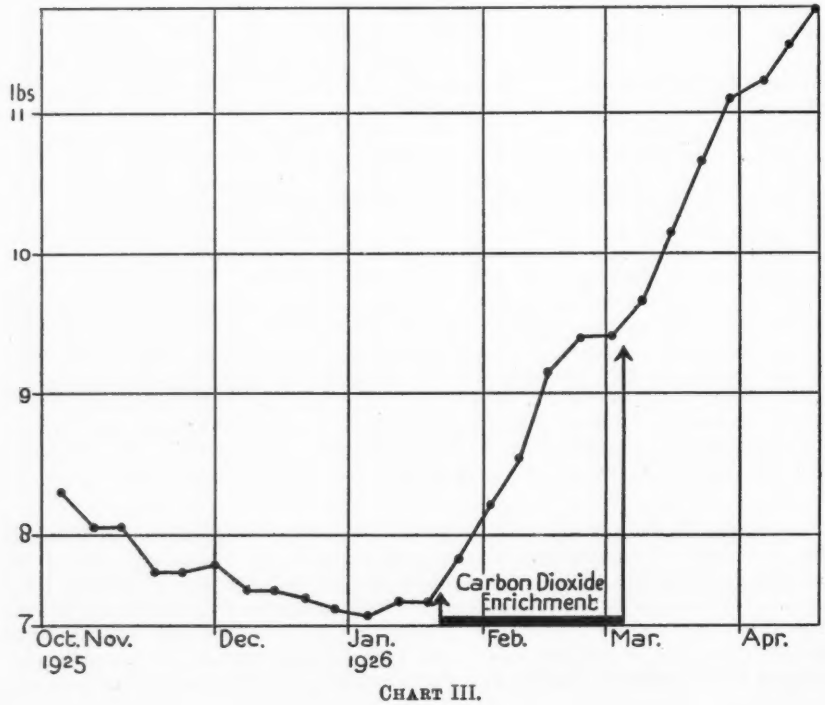


CHART III.

were gained and a further 23 oz. within the following seven weeks, after which he was discharged (see Weight Chart IV). He was then well nourished and active, his colour was good and he was taking food well.

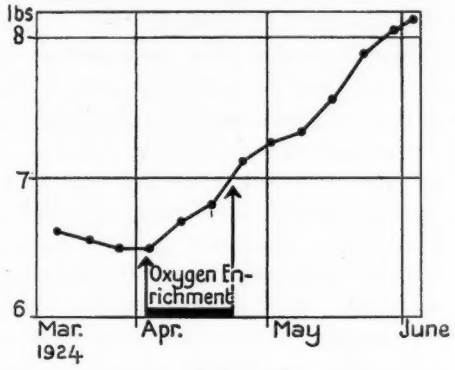


CHART IV.

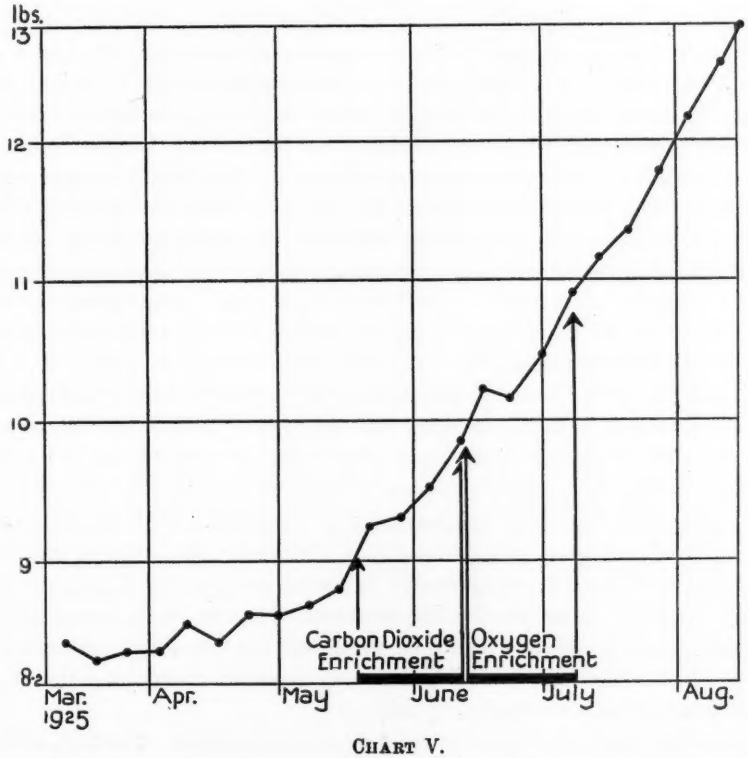


CHART V.

Case 15. M. B., a female child, aged 9 months, weighed 8 lb. 7 oz. on admission; she was small but well nourished, took her feeds well, and showed no dyspepsia. After nine weeks of various kinds of treatment she had gained 10 oz. in an unsteady fashion; she was then placed in the cot, without oxygen

enrichment, for three weeks and gained 13 oz. during this time, a subsequent three weeks in the cot, with oxygen enrichment, produced a gain of 11 oz., and over 2 lb. were added before discharge six weeks later (see Weight Chart V). The ammonia coefficient before cot treatment was 8·1, after the first three weeks' treatment 6·4, and at the conclusion of treatment 4·1.

Among the preliminary treatments tried unsuccessfully in these cases were included diets of cow's milk, Benger's food, breast milk, lactified milk, and the administration of cod-liver oil, vitamins, and glandular extracts; massage, electric treatment, sunshine, and ultra-violet rays.

Of the twenty-one cases subjected to cot treatment all save one, Case 5,[2] have responded in some degree, as judged by increase in weight and improvement in their general condition, and the great majority have benefited in a remarkable manner. In a small number of the earliest cases the objection may possibly be raised that perhaps all other methods of treatment had not been exhaustively tried; such a contention cannot, however, be admitted in the greater proportion of the cases. The number of infants treated and the uniformity of the results also serve to rule out the factor of coincidence. Occasionally an atrophic infant, after a long period of equilibrium, will suddenly and for no apparent reason, begin to gain weight. It is, however, more usual for the reverse to happen, death occurring within a few days after a rapid decline in weight and general condition. From the experience gained in treating the cases described, we are unable to ascribe the improvement to any other factor than the increased carbon dioxide (and in some cases oxygen) in the air breathed. Comparison of the rate of progress made with and without oxygen enrichment does not point decisively to either excess of oxygen or the raised percentage of carbon dioxide being the deciding factor in the good results. On the whole, however, progress appeared slightly more rapid when both oxygen and carbon dioxide were increased, so that the conclusion is that an increase in both oxygen and carbon dioxide is the most beneficial.

In addition to the series of twenty-one cases which form the basis of this paper, three other infants were selected as being typical instances of 'anoxaemic atrophies'. These children had completely failed to respond to the usual methods of treatment, and their urinary and 'alveolar air' analyses corresponded closely to those of the other cot cases prior to treatment. Of these three, one, after weeks of stationary weight, suddenly commenced to improve, and the urinary and 'alveolar air' analyses approximated more closely to the normal; the only apparent cause for the improvement appeared to be prophylactic injections against whooping-cough. Of the remaining two cases one suddenly began to lose weight rapidly and died for no apparent reason, and the other contracted measles and succumbed to this.

The urinary analyses in the cot cases all showed, without exception, a high ammonia coefficient (over 7·4) prior to treatment, while afterwards it fell considerably, usually to about 4, which was the average figure obtained in normal control cases. So far 'alveolar air' analyses have only been carried out in three

[2] This infant was only treated in the cot for one week.

of the cot children, but in all these the carbon dioxide percentage was below 5 per cent. prior to treatment, while afterwards it rose by approximately one-fifth of its initial value and reached a figure found in normal infants.

The following is a brief summary of the results obtained in the cases not described in detail above :

Case No.	Initial Weight.		Duration of Treatment Pre-cot.	Weight Pre-cot.		Gain in Cot.	Period in Cot.	Subsequent Gain.	
	lb.	oz.	days.	lb.	oz.	oz.	Days.	oz.	days.
1	7	7	28	7	11	17	25	19	(33)
2	6	15	30	6	7	12	21	11	(20)
3	8	7	21	8	4	5	30	27	(38)
4	9	0	28	9	5	16	23	15	(19)
5	5	10	28	5	6	no change	7	18	(30)
7	4	0	28	4	1	14	25	34	(50)
8	9	4	39	9	4	12	23	18	(27)
9	10	4	22	10	4	22	43	9	(12)
10	6	0	6	6	0	20	32	3	(5)
11	7	4	41	7	3	25	44	28	(37)
12	5	1	31	5	6	15	66	15	(55)
13	4	8	115	6	5	14	47	20	(85)
14	5	2	114	6	12	20	58	20	(85)
16	9	0	73	9	6	29	18	18	(23)
17	5	10	50	5	9	8	40	35	(123)
21	8	11	83	9	2	28	46	17	(25)

In Cases 1–5 (inclusive) and Cases 7, 8, and 17, the atmosphere was enriched with oxygen (40 per cent.) and carbon dioxide (2–3 per cent).

In Cases 9–16 (inclusive) the atmosphere was at first enriched only with carbon dioxide (2–3 per cent.) and later with oxygen (40 per cent.) in addition.

In Case 21 the atmosphere was never enriched with oxygen, but only with carbon dioxide (2–3 per cent.).

We wish to express our thanks to the Medical Research Council for a grant in aid of this work.

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THE QUINIDINE TREATMENT OF AURICULAR FIBRILLATION[1]

By JOHN PARKINSON and MAURICE CAMPBELL

The treatment of auricular fibrillation with digitalis is so satisfactory that its shortcomings are apt to be forgotten. It acts by reducing the rate of the ventricle and perhaps directly by increasing its efficiency; it does not, however, restore the action of the auricle, and the ventricle remains irregular.

Digitalis has been used in the treatment of heart failure since Withering's time, and more recently Mackenzie identified auricular fibrillation as the variety which gives the strongest indication for its use. He also showed how failure in patients with this irregularity could often be postponed for years by continuous treatment with digitalis.

When Frey (6), following up an observation of Wenckebach (19), found that quinidine could restore normal rhythm, he discovered an alternative to digitalis in the treatment of fibrillation. Since then opinion has passed through three stages—the first of enthusiasm following the confirmation of Frey's work; the second of disappointment when the risk of misadventure and the frequency of relapse in unselected cases became realized; and the third of discrimination in the choice of patients, where the danger may be least and the probable advantage greatest.

Our object has been to assess the value of quinidine in hospital and private practice, and to see what advantages it may possess. We have studied 20 patients with paroxysmal, and 44 with established fibrillation, in whom quinidine seemed more appropriate than digitalis. As they were selected as occasion arose during five years, it is obvious that only a small proportion were thought suitable for this treatment.

Quinidine sulphate was given by mouth in friable tablets of 5 gr. (0·33 grm.). In paroxysmal cases the dose was most often 5 gr. twice daily. In established cases the method adopted was a trial dose of 5 gr., and then doses increasing by 5 gr. daily until 30 gr. a day was taken. Quinidine and digitalis were not given at the same time. When the patient had congestive failure, digitalis was given first, and quinidine after an appropriate interval.

[1] Received October 2, 1928.

Selection of Cases.

A. *Paroxysmal fibrillation.* Quinidine was used whenever the paroxysms were frequent enough and long enough to be a serious disability, the object being to abolish the attacks or to diminish their incidence or duration. The number of years during which the patient had been liable to attacks and the size of the heart were not such important factors as in established fibrillation. Occasionally it was employed in an isolated long attack with the object of terminating that attack. Serious cardiac symptoms between the paroxysms were held to be a contra-indication to the use of quinidine, but otherwise it was generally used where the attacks were of distressing frequency.

Of the twenty patients, seven had mitral stenosis or a rheumatic history, and most of these were between 40 and 50. Three had mild exophthalmic goitre of several years' standing, and one an old simple goitre. Nine were without rheumatic or thyroid disease, and in two only the blood-pressure was just above the upper limits of normal, i.e. 160/100. There were none of the younger patients under 40, who were found in the corresponding group with established fibrillation.

B. *Established fibrillation.* In selecting patients with established fibrillation as suitable for treatment with quinidine, attention was paid to the aetiology, to the duration of fibrillation, and to the clinical condition, especially the size of the heart and the signs of failure.

(1) *Aetiology.* The aetiology is not generally thought of much importance in judging whether the result will be successful or not; but in published cases the rhythm has returned to normal in a rather higher proportion of cases without than of those with rheumatic valvular disease—in 76 instead of 61 per cent. (18), 68 instead of 53 per cent. (8). It has also kept normal for longer in those without rheumatic heart disease—in 40 as against 28 per cent. 'for some months or up to the time of writing' (8); in 43 as against 27 per cent. 'for varying intervals up to ten months' (18). In fibrillation associated with thyroid disease there has been a high proportion of successes, but with active hyperthyroidism these have often been temporary unless the hyperthyroidism could be relieved.

Among these forty-four patients there was mitral stenosis or a rheumatic history in twenty-four, all but three of these having disease of the mitral, and six of the aortic valve as well. Most of these were between 20 and 40. Six patients had a goitre, all without active hyperthyroidism at the time: they were aged 50–60.

There were fourteen patients without rheumatic or thyroid disease, mostly above 50 years. Of the five younger than this, the blood-pressure was normal in two, and borderline or rather high for their age in another two; in Case XXXIII it had risen four years later, though he was still in excellent health, so that longer observation will be needed to decide if these patients were really free from cardiovascular disease other than the arrhythmia. As would be expected from the aetiology of cardiac failure with normal rhythm (15), high blood-pressure and

syphilitic heart disease were noticeable for their rarity: in only two of the older patients was the blood-pressure above normal.

(2) *Duration of fibrillation before treatment.* Several authors have emphasized the importance of a short history in making a favourable result more likely. Convincing figures have been given by Viko, Marvin, and White (18), who found that where the duration of fibrillation was less than two months, normal rhythm was maintained during the period of observation in 70 per cent., but where it was two years, only in 13 per cent. In this series the time when a patient suddenly became incapacitated was assumed to be the onset of fibrillation. Sometimes he was already under observation and the date could be fixed with greater certainty; sometimes he could only say that he became worse, say, about six months ago, and that was taken as the probable date. The duration of fibrillation was from eight to twenty-seven days in eight of these patients and about a month in five others. In eighteen it was from three to six months, in seven from six months to a year, and in six more than a year.

(3) *Clinical condition of the patient.* The degree of congestive heart failure and the size of the heart are here the most important factors. Only a quarter of those who had failure, but more than half of those who had not, maintained normal rhythm (18). The better results in patients with little or no cardiac enlargement were emphasized by Hay (8) and Clark Kennedy (4). The previous occurrence of an embolus is generally accepted as a contra-indication to quinidine treatment, and no cases with a history of embolism were treated in this series.

The signs of congestive failure were absent at the time of treatment with quinidine in twenty-six, but there was slight oedema of the feet or enlargement of the liver in thirteen, and more severe failure in five.

The size of the heart was nearly always measured by radioscopy or orthodiagram, and in most cases it was not greatly increased. In seven there was no evidence that it was enlarged at all, in twenty-four it was slightly, and in thirteen considerably enlarged.

There were six patients who might have been excluded on the length of their history—three in whom there were successful results and three in whom there were not. There were seven who might have been excluded because of cardiac enlargement or congestive failure, the three unsuccessful ones just mentioned (Cases LI, LIX, and LXIV) and four others, of whom two gave good results. Apart from the three who could have been excluded on both grounds, our patients formed a fairly homogeneous group, very different from those most often found in a general hospital with large hearts and gross failure. This probably explains the difference between our conclusions and the pessimistic ones of Levine and Wilmaers (11).

Results of Treatment.

A. *Paroxysmal fibrillation.* Quinidine, it is generally agreed, is specially indicated in this group. Parkinson and Nicholl (16) reported diminution of

attacks in three of five patients, and concluded that quinidine was the treatment of choice. Smith and Clarke (17) found it useful, but thought it should not be given unless the paroxysms recurred every two weeks or more. Many favourable reports have been published (1, 7, 8, 12, 18).

Twenty cases of paroxysmal fibrillation were treated, but in the last two the attacks were too infrequent for us to reach any conclusions. In nearly all a pharmacological effect in reducing the length or frequency of attacks was observed, and in fourteen this was enough to produce clinical improvement.

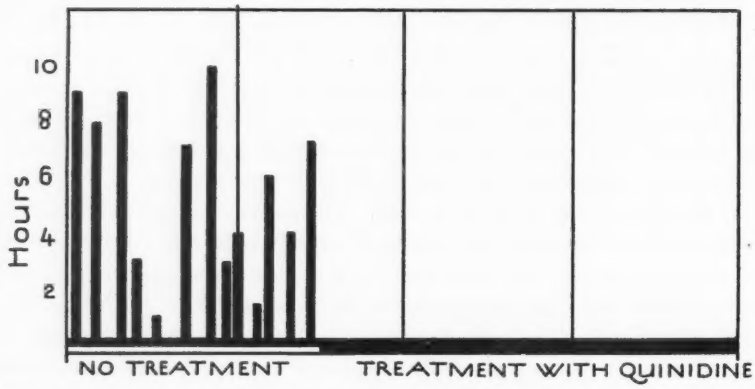


FIG. 1. The frequency and duration of paroxysms of fibrillation in Case I during twelve months, for the last seven and a half of which he was taking quinidine. There had been attacks for ten years of gradually increasing frequency. Abscissae, attacks during twelve months; ordinates, the length of attacks in hours.

In nine (Cases I–IX) the advantage was maintained for as long as they were under observation, for periods from six months to four years. The results were specially striking in the first four (e.g. see Fig. 1), but in three others the attacks were not stopped entirely. In all but two there had been frequent paroxysms such as, not infrequently, end in established fibrillation. Case IX developed fibrillation after a rough crossing from France. His pulse became regular after the first dose of quinidine, and four years later he had kept without atttacks and was able to lead a busy life. The absence of paroxysms for so long without treatment is exceptional, and fibrillation might have been perpetuated had he not been treated with quinidine. Case X was interesting as a spontaneous cure after natural recovery from exophthalmic goitre.

In five (Cases XI–XV) quinidine gave only temporary relief. In four (Cases X and XVI–XVIII) it proved of no real use, though it seemed to stop single attacks sooner than they would otherwise have ended. None of these four took quinidine regularly and for long enough to make an exact comparison feasible, but this in itself is evidence that they did not derive any material benefit from taking it. In four of these nine fibrillation became established, in three after digitalis and in one spontaneously.

In conclusion, complete relief was obtained in six and great diminution in

the number of attacks in three others—the period of observation varying from six months to four years. In four particularly the capacity for work and for the enjoyment of life was enormously increased. There was improvement for a few months only in five, and no appreciable relief in another four.

These results justify the view that quinidine is the most valuable treatment for paroxysmal fibrillation. This is specially true in the absence of other cardio-vascular disease, though its use is not limited to such patients.

B. *Established fibrillation.* In more than half of the published cases of established fibrillation treated with quinidine, normal rhythm has been restored. Thus in Hay's collection of 265 cases this occurred in 59 per cent. (8), in Burwell and Dieuade's collection of 600 cases in 56 per cent. (3), and in shorter personal series in 55 per cent. (17), 52 per cent. (9), 62 per cent. (10), and 68 per cent. (18). Sometimes successful results have been obtained in an even higher proportion of cases, up to 90 per cent. (3, 4, 5). Thirty of our forty-four patients (68 per cent.) regained normal rhythm, and in a large proportion it is still maintained after more than two years.

The duration of fibrillation before treatment seemed the most important factor in judging whether a favourable result was likely. When the onset was recorded as within a month it was always satisfactory, i. e. in ten normal rhythm persisted after twenty months (average) and in two relapse took place after thirty-one and twenty months. The only exception was Case LIV with acute rheumatism at the time.

TABLE I.

The Influence of the Duration of Fibrillation before Treatment on the Result obtained.

	Probable duration of fibrillation before treatment.		
	One month or less.	More than one but less than six months.	More than six months.
Normal rhythm restored and still maintained	10	10	3
Normal rhythm restored but not maintained	2	2	3
Normal rhythm not restored	1	6	7

The longer the duration of fibrillation the smaller was the chance of restoring normal rhythm and of maintaining it, if restored. Its onset in a patient in fairly good health should be regarded as a medical emergency usually requiring immediate treatment with quinidine, and the earlier this treatment can be started the better.

The patients without rheumatic or thyroid disease did much better than those with these conditions. Not only did a larger proportion regain normal rhythm, but all still maintain it after an average time of two years.

TABLE II.

The Influence of Aetiology on the Result of Treatment.

Aetiology.	Normal rhythm restored and still maintained.	Normal rhythm restored but not maintained.	Normal rhythm not restored.
Mitral stenosis or a history of rheumatic fever	9	5	10
Long-standing goitre (no active hyperthyroidism)	3	2	1
Other conditions	11	0	3

Even when patients with gross failure and large hearts were omitted, the results were better when there was less evidence of heart disease. Of those where the heart was normal in size, only one in seven failed to get normal rhythm; of those where it was slightly enlarged, one in four failed; and of those where it was considerably enlarged, one in two failed. There was the same difference if the patients were divided according to the degree of congestive failure. Only two of the five with more severe failure got normal rhythm, and the results were better in those with no signs than in those with slight signs of failure; yet there were ineffective and good results in both groups.

Age has not generally been thought an important factor, and the average age of our successful and unsuccessful cases was almost the same, both in the rheumatic and non-rheumatic groups. The presence of multiple lesions such as aortic and mitral disease was not of importance in itself, except in so far as such patients were more likely to have enlargement of the heart.

The usual method of quinidine administration was as follows: after a trial dose of 5 gr. the first day, the same dose was repeated twice the second day, three times the third day, and four times the fourth, the single dose being 5 gr. until the fifth day, when the doses were 10, 5, and 10 gr., and 10 gr. t.i.d. on the sixth day. This was continued for three or more days unless the rhythm had already become normal. The patient was kept in bed during the course of quinidine and for one week after. The effective dose was quickly reduced to 5 gr. t.i.d., on which the patient was generally discharged from hospital, unless a smaller dose than this had proved effective in the first place.

Six of our patients attained normal rhythm when they were having 10 gr. of quinidine a day or less, three on 15 gr., nine on 20 gr., five on 24–28 gr., six on 30 gr., and only one on 35 gr. a day, a dose seldom used. Where fibrillation had not been established for more than a month it was often arrested with small doses; and yet when the conditions were most favourable and the final result satisfactory larger doses were sometimes needed, or perhaps success was achieved with a small dose in a less promising case.

The amount of quinidine taken on the day of the change is important in deciding the best method of dosage. In reported cases fibrillation has most often stopped on the third to fifth days with 20–30 gr. a day, but sometimes after very small and sometimes only after much larger quantities.

The doses have often been given at two-hourly intervals because the maxi-

mum effect is produced after two hours, but as this lasts another hour and only falls off gradually during the next twenty-four hours (13) there does not appear to be any great advantage. In Jamieson's series and in ours, where the daily dosage was more distributed, there were as many successes without any increase in the total amount taken or in toxic effects. By analogy with digitalis and its cumulative action the dosage is often expressed as a total of so many grains, and we have therefore recorded this. But since the effects of quinidine pass off in 24–30 hours, it is more informing to express the effective dose as so much daily. The exact method of administration is not of paramount importance, but quinidine should not be increased too quickly up to the maximum, for the toxic effects were greater than usual where 30 gr. were given on the second day (17). If the first course of treatment fails, a second course may succeed.

In fourteen of the forty-four cases quinidine was unsuccessful. Three of these fourteen should not have received quinidine, as fibrillation had been present for more than a year and there had been gross congestive failure. Except in these three and in Case LXII (see later) the conditions seemed suitable, but normal rhythm was not obtained. Quinidine had to be stopped either for toxic symptoms or because it seemed to be without effect.

Persistence of normal rhythm. It is not enough to know that in half the patients with fibrillation normal rhythm will return; what matters most is to secure its restoration for a reasonable period of time. Published evidence about this is less complete, for as yet there has hardly been time enough to warrant more than general statements, e. g. '25 per cent. maintained for some months, two patients for more than two years' (9), 'some good results for more than a year' (5), and 'in selected cases 50 per cent. for six months or more' (3). In Clark-Kennedy's series 38 per cent. were known to be normal after three months and only 15 per cent. after nine months; but these were unselected cases and the final figures would be better, as several patients had not then been followed for long (4). In cases treated by members of the Cardiac Club, normal rhythm was maintained 'for some months or up to the time of writing' in 34 per cent. (8), and in those treated by Viko, Marvin, and White 'for varying intervals up to ten months' in 34 per cent. (18).

In this series the rhythm is still normal in 52 per cent. Twenty-three of our forty-four cases were normal when last seen or heard of, though four of these had suffered short temporary relapses which were easily stopped again by quinidine. In all it has already persisted for more than six months, in thirteen for more than two years, and in three for more than four years, the average duration being 27 months (see Fig. 2). In the seven others, who have permanently relapsed, the average duration of normal rhythm was 18 months.

The after-treatment may help to settle for how long and in what doses quinidine should be continued. The general opinion, for which there is not much tangible evidence, is that eurhythmia is more likely to be maintained with long use of small doses, such as 5 gr. twice a day, and that trouble is rarely caused by these amounts (8, 18).

Special attention has therefore been paid to this question. Of the seven who reverted to fibrillation, four were not taking quinidine at the time, and in three of these four, stopping it may have been of importance. Case XLVIII left off his quinidine against instructions after a month; he relapsed after three months. Cases XLV and XLVII kept well with quinidine for sixteen and twelve months respectively, but relapsed four and three months after it was

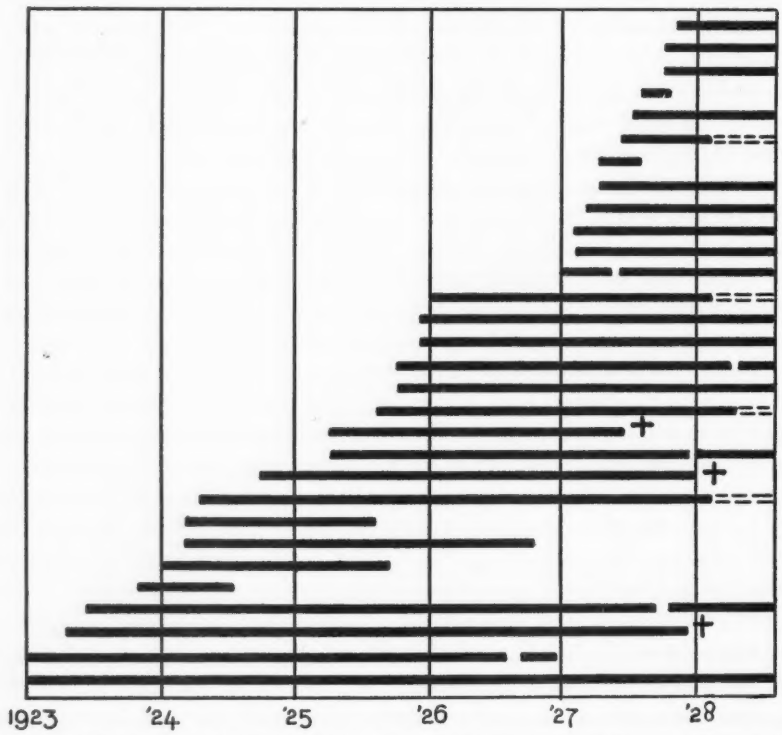


FIG. 2. The period of normal rhythm in the thirty cases where it was restored. The twenty lines reaching the right-hand side represent those who still maintain normal rhythm (four shown by the dotted lines were last seen early this year). The ten lines which stop before this represent seven who reverted to fibrillation and three who died, marked +. The short gaps represent the four temporary relapses. Abscissae, duration in years; ordinates, individual cases.

stopped. In these three relapse came soon after stopping quinidine and might have been postponed by its use, but Case XLVI maintained normal rhythm for eighteen months after she stopped taking it. In the remaining three relapse took place while they were taking quinidine.

There were also four temporary relapses which were instructive. Case XXX took quinidine for four years and relapsed five weeks after stopping it; he responded to quinidine treatment a second time. In Case XLII it was reduced to five grains daily after three months and fibrillation returned in six weeks. Normal rhythm was retrieved and still persisted a year later with twice that dose.

Cases XXI and XXXIV remained in good health with normal rhythm for a year or more with quinidine and for the same period without it; on retaking quinidine fibrillation was stopped for a second time, with great advantage.

Among these eleven with relapses there was a high incidence of goitre and mitral stenosis, which suggests the importance of continuing quinidine in these conditions. After the return of normal rhythm, quinidine should be continued in doses such as 5 gr. t.i.d. for one month, b.i.d. for six to twelve months, and once daily for a year. Where there is mitral stenosis or goitre, small doses should be taken indefinitely. Five grains t.i.d. for three years and b.i.d. for four, five, and six years were taken without any untoward symptoms. Should a relapse take place a second course of treatment should be given and will often succeed.

Clinical advantages. After the restoration of normal rhythm most patients were much better, whether judged by their comfort or by what they could do. Many benefited so much that it is difficult to think they could have felt as well or done as much with the help of digitalis. They were enormously better than when they first came under observation, some after digitalis treatment. Their symptoms returned at once if they relapsed, and generally they were keen to be treated with quinidine a second time.

The following cases illustrate their capacity after treatment. Case XXXIII was at work in good health after five years. Case XXX had endured for five months increasing dyspnoea and constriction in the chest. Normal rhythm was restored and maintained for over four years, when he was in good health and hardly short of breath, till he got up one morning with a return of the old symptoms and found his pulse again irregular. Normal rhythm was retrieved with advantage for the second time. Case XXXI had good general health after four years. Case XLIV had been breathless for three years and from time to time confined to bed. Normal rhythm was restored and maintained for nearly four years, during which time she married and did much of her ordinary housework. A relapse to fibrillation was at once followed by cough and breathlessness, from which she had been almost free while she had normal rhythm: nor has digitalis succeeded in keeping her so well.

Other patients have not yet been observed for so long, as it is only five years since the first was treated; but among those who have kept normal rhythm for more than two years are Case XXXIV leading an energetic life which entails travelling about London most of the day; Case XXXV in active charge of several branches of a large business; Case XXI doing heavy gardening after his work as a schoolmaster; Case XXVIII playing golf in addition to a long day's work; and Case XXXVI discharged from the R.A.F. on this account, but now able to play hockey and do all he wants.

Case XXIV, maintaining normal rhythm without any improvement nearly, if not quite, up to the time of her death, was the only patient who was not better for it. Case XXII remained in excellent health for four years; then he became ill and three months later died of infective endocarditis, normal

rhythm persisting. Would he have been less likely to develop this if he had not been relieved of his fibrillation? It is difficult to think so, but it is certainly rare for the two conditions to occur together (14, 15).

The history of another man may be given as, when described by Parkinson and Nicholl (16), it was not long since he had regained normal rhythm. After rheumatic fever in childhood he was well enough to be in the army at Salonika when 42 years old, though he had mitral stenosis and a large heart; fibrillation probably started then, as he became very breathless with an irregular pulse. At 45 he had three hemiplegic attacks, from which he made a good recovery except for blindness in the right eye. When he was 47, with some hesitation on account of the history, quinidine was given and normal rhythm was restored. Six years later he was in good health, walking several miles a day, and during the general strike bicycled up from Tonbridge for quinidine, as he himself was keen on taking it after seeing a friend relapse on its omission. An orthodiagram of his heart in 1928 was almost identical with one taken in 1922.

Most of these patients felt better and were able to do more than with digitalis treatment. Many sufferers from heart disease enter on a more rapid downward course from the onset of fibrillation, and it is undoubtedly the most serious turning-point in their lives; the after-history must be judged by comparison with this.

It is not too much to believe that when quinidine postpones this turning-point it adds at least some of the period of normal rhythm to their expectation of life. As a comparison, admittedly an inexact one, six of the fourteen unsuccessful cases are known to be dead, but only three of the thirty where quinidine succeeded.

The Ill-effects of Quinidine.

There are three dangers which must be shortly reviewed: (*a*) toxic effects, (*b*) embolism, and (*c*) sudden death from one or other of these causes.

(*a*) Apart from occasional headache, deafness, palpitation, or diarrhoea, quinidine had to be stopped in some patients because such symptoms became pronounced. Severe toxic effects were found in Case LXII with complete heart-block, which is a contra-indication to quinidine (2). Thirty grains a day led to normal rhythm with increased ventricular rate and then to flutter. Three days later he had an attack with cyanosis and unconsciousness, whereupon quinidine was discontinued and fibrillation and complete heart-block returned. In a girl with acute rheumatism (Case LIV) three doses of 5 gr. of quinidine induced vomiting and collapse with rigors and an increase in the size of the liver within twenty-four hours. Digitalis subsequently proved useless, the patient getting worse and dying a month later—less than two months after the original onset of fibrillation. This shows the need for care in the use of quinidine with an active rheumatic carditis.

In Case LXI quinidine induced flutter which persisted after 30 gr. daily, and after digitalis treatment, but with this 4 : 1 block was obtained and he was able

to return to work. In Cases XLVII, LI, and LVIII flutter was noted, but did not persist.

(*b*) The chance of clots being detached as emboli when the auricles resume their rhythm has, we think, been over-emphasized. Embolism is a common event in others with mitral stenosis and fibrillation, either under treatment with digitalis or not under treatment at all. It was found in 4 per cent. of cases not treated with quinidine, and in 3 per cent. of cases so treated (18); in 554 of such cases which we have abstracted from the literature, emboli occurred in 4 per cent., often with only transient effect. Moreover, the change to normal rhythm in cases of paroxysmal fibrillation habitually takes place without mishap.

None of our cases of established fibrillation had an embolism when their rhythm changed to normal and only two when they were taking quinidine. Case LI became dangerously ill with flutter and copious haemoptysis, probably due to multiple small emboli, but recovered quickly. Case XXIII, one week after the return of normal rhythm, had an embolism of the leg which left no disability.

The same man, when normal rhythm had continued for a year without quinidine, had a second embolism, and Cases XV, XLVI, XLVII, and LII, all with fibrillation, had emboli while being treated with digitalis. In addition, Cases VI and XIII with paroxysmal fibrillation had emboli; though the former was having quinidine there was no reason for associating it with her attack, and the latter was having digitalis at the time.

When the auricle is not contracting the blood becomes stagnant in its periphery, favouring the formation of a mural thrombus and so of a potential embolus. This is most likely to occur with long-standing fibrillation and with large auricles, and it is clearly advisable to postpone this added risk as long as possible. But such cases are not suitable for, and were not chosen for, quinidine treatment, and if patients are properly selected this danger is slight. Further, the return of normal rhythm is calculated to prevent just those conditions which are liable to lead to thrombosis in the auricles.

(*c*) The chance of sudden death in some one relatively well has to be carefully weighed against the probable advantage—precisely as when advising an operation. Failure of the respiratory centre or of the ventricular muscle seem to constitute this danger. Death was reported in 1 per cent. of 484 collected cases treated with quinidine (18); but we have found it in nearly 4 per cent. of 554 cases (including those reported by Hay (8)). Hardly any of these deaths were proved to be due to emboli, and in most of them necropsy showed no obvious structural disease to account for it. Death has occurred not only after large doses, but almost at once after small or moderate doses (8, 9), whether normal rhythm has been restored or not.

Three patients who developed alarming symptoms have been discussed. In addition, we have to record one death in our series of 64 cases (Case LXIII). Conditions seemed suitable for quinidine treatment and her pulse became regular on the tenth day; yet she died suddenly the following afternoon. Looking back,

we can find nothing to point to any special danger in her case, but there was no necropsy and the size of the heart had not been determined by X-ray examination on the only occasion she had been seen.

We must, however, mention a man encountered since this paper was written. He had been treated for syphilis when 28, and for congestive failure with fibrillation when 43. As the Wassermann reaction was found positive three months later, he was also given mercury and iodide. There was an enlarged heart with an aortic systolic murmur (an aortic diastolic murmur was heard once). He was admitted for quinidine treatment, and on the eighth day (the third day with quinidine gr. 10 t.i.d.) when the pulse was still irregular, he suddenly collapsed and died. *Post mortem* there was no embolism; but the heart weighed 17 oz., and there were calcareous plaques on the aortic valves. There had been an increase in the ventricular rate to 180, which might have led us to stop quinidine. In view of this case and one reported by Jamieson (9) the treatment of a patient with syphilis should not be undertaken lightly.

Summary.

Nine out of eighteen cases of paroxysmal fibrillation were much improved by quinidine treatment, the attacks being abolished or greatly reduced for as long as the patient was under observation; in one quarter the advantage was only temporary and in the remainder there was no improvement at all.

In forty-four selected patients with established fibrillation normal rhythm was restored in thirty, i.e. 68 per cent. The remaining 32 per cent. failed to respond to quinidine.

In twenty-three of them—more than half of all who were treated—normal rhythm was not only restored, but was still maintained after an average period of more than two years, and once after five years. Four of these patients had short temporary relapses, which were readily brought to an end with quinidine. The other seven of the thirty successes kept well for an average period of eighteen months before they reverted to fibrillation. Relapses were more likely to occur on omitting or reducing quinidine.

With two exceptions, all patients were strikingly better for the return of normal rhythm; some were much better than they had been previously when taking digitalis, and many are now leading such active lives that it is difficult to think they could have been equally well with digitalis treatment.

The results were best of all where there was no rheumatic valvular disease and no hyperthyroidism; for all those in whom the arrhythmia was the only evidence of heart disease still have normal rhythm after an average period of two years (Table II).

Severe toxic effects were seen in two patients. Embolism, which occurred in two others but left no permanent disability, was found no more frequently under quinidine than under digitalis treatment. One patient died suddenly while taking quinidine.

In paroxysmal cases the usual dose was 5 gr. of quinidine two or three times a day. Established cases were kept in bed and the dose was generally raised by 5 gr. daily to 10 gr. three times a day, unless normal rhythm was restored with a smaller dose. This took place most often with 20–30 gr. a day.

Conclusions.

Quinidine is the best treatment for paroxysmal fibrillation whenever the attacks are of such length or frequency as to justify continuous medication, provided the patient is well enough in the intervals; its use for this purpose is devoid of risk.

When established fibrillation is of recent onset quinidine is the treatment of choice, and it is important that it should be used at once. In the absence of serious failure or much cardiac enlargement it is likely to give better results than digitalis, as it often restores normal rhythm, even for some years, with remarkable freedom from symptoms.

When fibrillation has been established for more than six months, when there is a large heart or gross congestive failure, or when there is active rheumatic or syphilitic infection, there is more danger in using quinidine and less chance of lasting success. Digitalis is then the best treatment and quinidine should seldom be used. Between these extreme groups the question of using quinidine must be decided in individual cases and with a leaning to digitalis.

With no evidence of heart disease other than the arrhythmia the after-treatment with quinidine may be short, but with rheumatic or thyroid disease it should be prolonged. Should a relapse occur, a course of quinidine may properly be repeated, indeed many patients will demand it.

The particular merit of a success with quinidine lies in the avoidance, or at least in the postponement, of fibrillation with its tendency to failure and its risk of embolism. It may well increase the expectation of useful life, limited though it may be.

The onset of fibrillation in a patient enjoying good or even moderate health should be regarded as a medical emergency. Quinidine, if it is used at once, is generally a safe and effective remedy and normal rhythm may be maintained for years.

Case Histories.

The following abbreviations are used in describing the cases:

M., F. = male, female.
Q. = quinidine.
A.F. = auricular fibrillation.
P.A.F. = paroxysmal auricular fibrillation.
N.R. = normal rhythm.
B.P. = blood-pressure.
R.F. = rheumatic fever.
W.R. = Wassermann reaction.
EC. = electrocardiogram.

The size of the heart was generally determined by orthodiagraphy. There was no evidence of valvular disease, and no history of rheumatic fever, chorea, or

syphilis, if not mentioned. Blood-pressure is given in all cases without mitral stenosis or a rheumatic history, but in those, only where it was raised. It was measured during normal rhythm or after its restoration, except where qualified by the word approximately.

Each patient has been followed till June 1928 unless otherwise stated.

Paroxysmal Auricular Fibrillation. Cases I–XX.

Case I, M., aged 49. R.F. at 9 years. After diphtheria at 39, onset of paroxysms; at first each few months, then more frequently till twelve attacks in four months, averaging five hours each. Heart not enlarged, no signs of failure. B.P. 140/95. P.A.F. (clinically).

On 3 gr. Q. b.i.d. no attacks for one year. He wrote: 'The relief was even greater than the absence of attacks would show. Before taking it every meal gave me extra systoles, since have been almost entirely free.'

Case II, F., aged 73. Growing pains as child. Four years ago urgent dyspnoea for twelve hours with irregular pulse. Since then, often palpitation for a few minutes. Eighteen months ago second severe attack twelve hours, third attack seven months ago. Three attacks in last three months, each about twenty-four hours, with severe anginal pain. Heart slightly enlarged, slight oedema of feet. B.P. 180/90. P.A.F. (clinically).

Took 5 gr. Q. for six months and then 3 gr. Q. daily, no attacks for one year (February 1928).

Case III, M., aged 55. Goitre without hyperthyroidism since childhood. Frequent paroxysms for eight months; then one year without, after which they recurred nearly every day, often lasting hours. Heart slightly enlarged, some failure. B.P. 125/75. W.R. negative. P.A.F. (EC.).

With 5 gr. Q. b.i.d. no attacks for six weeks, oedema disappeared and able to walk five miles a day. Next three months about one attack each week, then attacks stopped, soon after which he took no more quinidine. Four years later in good health.

Case IV, M., aged 58. Attacks for one year, getting worse and more frequent. Heart slightly enlarged, slight oedema. B.P. 120/80. P.A.F. (EC.).

Took 3 gr. Q. b.i.d. for fourteen months, no further attacks, at work and feeling well.

Case V, M., aged 58. Fourteen years ago in hospital with rapid irregular pulse for a few days. Since then irregular attacks, last four months about one a week. Heart not enlarged, no failure. B.P. 120/85 rising to 175/95 a year later. P.A.F. (EC.).

On 5 gr. Q. b.i.d. no attacks for eight months, then four short attacks only in the next year.

Case VI, F., aged 48. Five years slight hyperthyroidism and attacks lasting 8–38 hours. Heart slightly enlarged; no failure. B.P. 185/85. P.A.F. (clinically).

Before Q. each week two attacks of about fourteen hours; on 5 gr. Q. b.i.d. for two months only five attacks of five hours. Then an attack of unconsciousness (? a small cerebral embolism) not associated with any change of rhythm. Two and a half years later, fairly well, occasional short attacks (January 1928).

Case VII, M., aged 67. Four years ago and six months ago attacks, lasting certainly one and possibly several days. Since then attacks of giddiness and a month ago fell in the street unconscious, but able to walk home later. Heart slightly enlarged, no failure. B.P. 150/90. P.A.F. (EC.).

On 5 gr. Q. b.i.d. for nine months, once daily for a year, and then on alternate days, no attacks for four years.

Case VIII, M., aged 58. Last two years five attacks of about six hours. Heart not enlarged, no failure. B.P. 150/90. W.R. negative. P.A.F. (clinically).

Two attacks of about seven hours each month for ten months, last six of which on 5 gr. Q. b.i.d. without effect. Then eight attacks in a month, after which a source of domestic worry was removed. Next five months only two attacks, all this time on 5 gr. Q. b.i.d. Now fifteen months with two attacks only, last ten months without quinidine.

Case IX, M., aged 54. Always good health. Very ill crossing from France, next day worse and pulse irregular. Heart not enlarged, no failure. B.P. not raised. P.A.F. (polygram).

After 5 gr. Q. pulse became regular, having been irregular six hours only. Took quinidine for a few days. Three and a half years later, in good health, active life, and no more attacks.

Case X, F., aged 39. Exophthalmic goitre nine years, active hyperthyroidism. Two years frequent paroxysms. Heart slightly enlarged, no failure. B.P. 150/80. P.A.F. (EC.).

First year under observation four attacks a month, about eight hours each. Took 5 gr. Q. daily for one week; no attacks, but would not continue because of headaches. Next six months one attack of about six hours each month; next year one similar attack each two months. Then thyroid almost normal, pulse-rate 90 instead of 110–130, attacks became less frequent. Ten months later her first child was born. Four years later in good health and no more attacks.

Case XI, F., aged 42. Twelve years exophthalmic goitre with occasional attacks, much worse last year. Heart slightly enlarged, no failure. B.P. 130/80. P.A.F. (EC.).

First observed attack of ten hours after hemithyroidectomy. Better after operation; few attacks for seven months. Then recurrence of almost daily attacks which were greatly reduced in frequency for two months with 5 gr. Q. b.i.d. Recently relapse and a further portion of the thyroid has been removed.

Case XII, M., aged 55. Two years paroxysms of half an hour once a fortnight, recently more often and longer. Heart slightly enlarged, no failure. B.P. 145. W.R. negative. P.A.F. (EC.).

On 5 gr. Q. t.i.d. attacks less frequent and severe for two months, then increasing for three months till nearly one a day. On digitalis attacks greatly reduced in frequency for last year.

Case XIII, F., aged 53. R.F. at 18 years. Four years ago attacks each three months. With Q. elsewhere no attacks nine months; Q. stopped, attacks recurred. Last year worse till four a month for eighteen to twenty-four hours. Heart slightly enlarged, oedema of feet. B.P. 190/100. P.A.F. (EC.).

Attack of four days stopped after second dose of 5 gr. Q., but next attack while on 5 gr. Q. b.i.d. Digitalis given; attack stopped next day, but pulmonary embolism the following day. Attacks continued next four months.

Case XIV, M., aged 60. Six years increasing frequency of attacks, at first each few months, finally once a week, lasting about eight hours. Heart slightly enlarged, no failure. B.P. 165/100, P.A.F. (clinically).

On 5 gr. Q. b.i.d. four short attacks in six months. Then increasing frequency till as bad as ever. Two years later still attacks in spite of digitalis (November 1927).

Case XV, F., aged 41. Chorea as child. Breathless twelve years, seven months paroxysms. Heart slightly enlarged, mitral stenosis, no failure. P.A.F. (EC.).

During ten weeks' observation five attacks of twelve to twenty-four hours; during ten weeks on 5 gr. Q. t.i.d. no attacks. Then stopped Q. because of nausea. Nine months later frequent attacks, digitalis established fibrillation. A year later small pulmonary embolism, but after two years still in fair health (March 1926).

Case XVI, M., aged 48. Six months paroxysms. Heart slightly enlarged, no failure. B.P. 145/90. W.R. positive. P.A.F. (EC.).

Three attacks first week in hospital, two stopped soon after 5 gr. Q. Attacks irregular, but twice when frequent 5 gr. Q. b.i.d. did not stop them. A year later A.F. after digitalis treatment; in fair health three years later.

Case XVII, F., aged 39. R.F. at 10 years. Four years frequent attacks made shorter by taking Q. Heart not enlarged, no failure. B.P. 110/70. P.A.F. (EC.).

N.R. after 10, 20, 5 gr. Q. on successive days, i.e. on seventh day. Took Q. for a few days only. Next three months, one short attack. To hospital tenth day of next attack. A.F. persisted in spite of Q. taken intermittently up to 20 gr. daily. Satisfactory progress with digitalis for eight months, when failure recurred (May 1927).

Case XVIII, F., aged 42. Chorea at 13 years. Two years attacks of increasing frequency, lasting about two days. Heart moderately enlarged, mitral stenosis, slight failure. P.A.F. (EC.).

On 5 gr. b.i.d. no attack for two weeks, then two short attacks next two weeks. Would not take Q. regularly after this, as she said it disagreed. A.F. established with digitalis, three years later fair health but some oedema of feet (May 1927).

Case XIX, M., aged 61. One year ago attack lasting twelve hours, recently again for thirty-two hours. Heart slightly enlarged, no failure. B.P. 160/90 P.A.F. (clinically).

Eight months later similar attack for twelve hours, which stopped soon after 5 gr. Q. Three and a half years free, but next attack lasted nineteen hours and did not stop till after 5 gr. Q. twice. Then two years without attack.

Case XX, M., aged 38. Chorea as child. Six attacks, lasting 24–48 hours the first with dysentery in Mesopotamia at 32 years. Heart not enlarged, no failure. B.P. 150/90. P.A.F. (EC.).

Next attack stopped after 5 gr. Q., which he continued for a few weeks. Eighth attack seventeen months later, for which he again took Q. Then two years free from attacks.

Established Auricular Fibrillation. Cases XXI–LXIV.

Normal rhythm still maintained. Cases XXI–XLIII.

A. *Rheumatic cases.*

Case XXI, M., aged 48. Two years breathless, six weeks worse, pulse irregular. Heart slightly enlarged, mitral stenosis, no failure. A.F. (EC.).

N.R. after 5, 10, 15, 20 gr. Q. on successive days (total 3·3 grm.). Took 5 gr. b.i.d. for eighteen months. Good health for thirty months. After recur-

rence treated himself (5, 10, 15, 20 gr. Q. on successive days) but stopped for palpitation. Heart as before, slight oedema. A.F. (EC.) Advised to stop Q. till in hospital, but took 20 gr. more (total 4·6 grm.) and came in three days later with N.R. Six months later in good health, taking 5 gr. Q. b.i.d.

Case XXII, M., aged 46. Three weeks palpitation and exhaustion. Heart slightly enlarged, mitral stenosis, no failure. A.F. (EC.).

N.R. after 5, 10, 15, 20, and 5 gr. Q. on successive days (total 3·6 grm.). Took 5 gr. b.i.d. for four and a half years. Well most of this time, but finally tired and unfit for anything. Infective endocarditis diagnosed and streptococcus longus grown from blood. Died two months later. No necropsy.

Case XXIII, M., aged 39. Chorea at 9 years. Six months too breathless to work. Heart slightly enlarged, mitral stenosis, no failure. A.F. (EC.).

N.R. after 5, 10, 15, 20, 10 gr. Q. on successive days (total 3·9 grm.). A week later (while on 5 gr. Q. t.i.d.) small embolism in leg; effects persisted a few days only. Failed to take Q. when discharged. Gave up work after five months for breathlessness. After nine months of N.R., second embolism with left hemiplegia. Some weakness of left side, N.R. still maintained after three years. Three months later, failure and death; no necropsy.

Case XXIV, F., aged 22. One year ago two severe fainting attacks of one and three hours (? P.A.F.), six months breathlessness. Heart moderately enlarged, mitral stenosis, no failure, N.R. (EC.). Later A.F. (EC.) which persisted three months.

N.R. after 3, 6, 9, 9, 9, 12, 15, 20, 30 gr. Q. on successive days (total 8·0 grm.). Took 5 gr. t.i.d. for seven months only. N.R. still maintained after two years, but little if at all improved. Died at home five months later; no necropsy.

Case XXV, M., aged 33. R.F. at 13 years. Under observation three years, good exercise tolerance. Onset of palpitation at tea, unable to do anything since. Heart moderately enlarged, mitral stenosis, slight failure. A.F. (EC.).

N.R. after 5, 10, 15, 15, 20, 20, 25, 30, 35, 25 gr. Q. on successive days (total 13·0 grm.) after twenty-seven days of A.F. Then 5 gr. t.i.d., which he still takes. After eight months, general condition as before onset of A.F., but last month three short paroxysms.

Case XXVI, F., aged 28. Chorea as child. Breathlessness and cough one year; worse two months. Heart much enlarged, mitral stenosis, moderate failure. A.F. (EC.).

N.R. after 5, 10, 15, 15, 15, 18, 21, 24, 28 gr. Q. on successive days (total 9·2 grm.). Q. then reduced to 5 gr. t.i.d. Eight months later in good health with N.R.

Case XXVII, F., aged 35. Heart affected at 5, but fairly well till 33 years. Extreme breathlessness five months. Heart moderately enlarged, mitral stenosis, general failure. A.F. (EC.).

Four months rest and digitalis; N.R. after 3, 6, 12, 18, 18, 18, 21, 24, 24, 24, 28 gr. Q. on successive days (total 12·7 grm.). Q. then reduced to 5 gr. t.i.d. Seven months later in fair health with N.R., much better than when treated with digitalis.

Case XXVIII, M., aged 22. Rheumatism at 12, quinsy and nephritis at 21 years. One year later irregular pulse and palpitation. Heart slightly enlarged, no failure. A.F. (EC.).

N.R. after 5, 10, 15 gr. Q. on successive days (total 2·0 grm.), i.e. on eleventh day of A.F. Took 5 gr. b.i.d, for a year, and then once daily. After three years N.R. still maintained; in good health, playing golf after a full day's work.

Case XXIX, M., aged 58. R.F. at 12 years. Twelve days before tired and run down, pulse found irregular. Heart slightly enlarged, no failure. B.P. 155/90. A.F. (EC.).

N.R. after 5, 10 gr. Q. on successive days (total 1·0 grm.), on eighteenth day of A.F. Took 5 gr. b.i.d. for six months. In good health, and abroad, after two years of N.R.

B. *Thyroid cases.*

Case XXX, M., aged 54. Small thyroid cyst, no hyperthyroidism. Five months dyspnoea and palpitation. Heart slightly enlarged, no failure. B.P. 140/90. A.F. (EC.).

N.R. after 5, 10, 15, 20, 10 gr. Q. on successive days (total 3·9 grm.). Took 5 gr. t.i.d. for three years, b.i.d. for six months and once daily for six months. Only five weeks after stopping Q., woke up with pain in chest and found pulse irregular. Treated himself, and pulse regular after 20 gr. Q. At present after another ten months (five years in all) N.R. and good health.

Case XXXI, F., aged 52. Five years ago exophthalmic goitre; better but poor walker since. Ten days palpitation and breathlessness. Heart slightly enlarged, no failure. A.F. (polygram).

N.R. on sixteenth day of A.F. after 5 gr. Q. on two successive days (total 0·7 grm.). Took 5 gr. b.i.d. for one year and 5 gr. once daily for six months. In good health and able to travel to Australia; N.R. maintained after four years (Jan. 1928).

Case XXXII, M., aged 49. Large firm goitre for many years, no hyperthyroidism. Three months very breathless. Still much disability after digitalis. Heart moderately enlarged, slight failure. B.P. 150/70. A.F. (EC.).

N.R. after 5, 10, 15, 20, 25, 30, 30, 30, 30, 30, 30 gr. Q. on successive days (total 16·6 grm.). Took 5 gr. t.i.d. for one month, b.i.d. for three months, and then once daily. Fourteen months later in good health with N.R.

C. *Other cases.*

Case XXXIII, M., aged 37. Three months palpitation and dyspnoea. During previous two years three attacks lasting one to seven days. Heart not enlarged, no failure. W.R. negative. A.F. (EC.).

After 5 gr. Q. on first day and 5 on second, flutter with 2:1 block (auricle 260); N.R. after 5, 10, 5 gr. on successive days (total 1·3 grm.). Took 5 gr. Q. b.i.d. for three years and still takes 5 gr. daily. N.R. maintained after sixty-six months, at work and felt well. B.P., which was 120, now 160/90.

Case XXXIV, M., aged 36. Six months exhaustion, pulse found irregular. Heart slightly enlarged, no failure. A.F. (EC.).

N.R. after 5, 10, 15, 20, 25, 30, 30, 10 gr. Q. on successive days (total 9·4 grm.). Took 5 gr. Q. t.i.d. for three months, b.i.d. for six months and once daily for six months. Two years later B.P. 160/90 (before 145/100), active business life with no symptoms; six months later (i.e. after eighteen months without any Q.) seen again eight hours after onset of A.F.; ill, tired, and unable to work. N.R. after 3 gr. Q. twice, maintained seven months, again with relief from symptoms.

Case XXXV, M., aged 40. Six months palpitation, cough, and exhaustion. Heart not enlarged, no failure. B.P. 155/95. A.F. (EC.).

N.R, after 5, 10, 15, 20, 25, 30, 30 gr. Q. on successive days (total 8·8 grm.). Took 5 gr. t.i.d. for one month, b.i.d. for one month, and once daily for the third month. At work without symptoms; N.R. maintained after three years.

Case XXXVI, M., aged 22. January 1925, passed for Royal Air Force; May 1925, fainted on parade and pulse found irregular. Heart slightly enlarged, no failure. B.P. 125/80. A.F. (clinically).

Two months later N.R. after ten days of Q., generally 5 gr. t.i.d. Took Q. one month only. Playing hockey and at work with N.R. three years later (December 1927).

Case XXXVII, F., aged 52. Ten years attacks of palpitation, for an hour, each month or two. Last nine days continuous palpitation and breathlessness. Heart not enlarged, slight oedema. B.P. 160/75, rising to 190/90, two years later. W.R. negative. A.F. (EC.).

N.R. after 5, 10, 15 gr. Q. on successive days (total 2·0 grm.) on thirteenth day after onset. Took 5 gr. t.i.d. for one year and then 5 gr. b.i.d. Some oedema of ankles, but able to walk several miles, i. e. in fair health with N.R. after two years.

Case XXXVIII, M., aged 55. Eight days 'fluttering of heart'. Heart not enlarged, no failure. B.P. 125/80. A.F. (EC.).

N.R. after 3, 5, and 5 gr. Q. on successive days (total 0·9 grm.), i.e. on twelfth day after onset. Took 5 gr. Q. b.i.d. for six months and then once daily. N.R. maintained, in good health, at work, and able to play golf after eight months (February 1928).

Case XXXIX, M., aged 58. Paroxysmal tachycardia for thirty years, four times a year, recently more frequent, generally for less than an hour. Twenty days ago sudden onset of irregular palpitation. Heart slightly enlarged, no failure. B.P. 125/70. A.F. (EC.).

N.R. after 5, 10, 15, 20, 10 gr. Q. on successive days (total 3·9 grm.) on twenty-seventh day after onset. Took 5 gr. b.i.d. for four months, then 3 gr. b.i.d. Still occasional tachycardia, but N.R. and good health maintained for fifteen months.

Case XL, M., aged 55. Five weeks palpitation and dyspnoea. Heart not enlarged, no failure. B.P. 130/80. A.F. (EC.).

N.R. after 5, 10, 15, 20, 25, 30, 30 gr. Q. on successive days (total 8·8 grm.). Took 5 gr. t.i.d. for one month and then b.i.d. Able to work all day, still with N.R., fifteen months later, but four paroxysms lasting less than a day.

Case XLI, M., aged 41. Two months ago nausea and diarrhoea, pulse found irregular. Heart not enlarged, no failure. BP. 110/75. W.R. negative. A.F. (EC.).

N.R. after 5, 10, 15, 20, and 10 gr. Q. on successive days (total 3·9 grm.). Still takes 5 gr. b.i.d. One year later walking twelve miles a day, N.R. maintained.

Case XLII, M., aged 55. Breathless one year, suddenly worse a month ago. Heart slightly enlarged, no failure. B.P. 150/100. A.F. (EC.).

N.R. after 5, 15, 18, 21, 24, 27 gr. Q. on successive days (total 7·2 grm.). On 5 gr. t.i.d. relapsed third day. N.R. again after 18, 21, 24, 27, gr. Q. (total 5·8 grm.). Took 9 gr. t.i.d. the first, 5 gr. t.i.d. the second, 5 gr. b.i.d. the third month and 5 gr. daily. A.F. after six weeks on this dose, but N.R. again with 5 gr. b.i.d. One year later, in good health, at work, with this dose. N.R. still maintained, sixteen months in all.

Case XLIII. M., aged 68. Ten months breathless. Heart slightly enlarged, general failure. B.P. 160/90. A.F. (EC.).

N.R. after 5, 15, 18, 21, 24 gr. Q. on successive days (total 5·4 grm.). Q. reduced to 5 gr. t.i.d., but A.F. returned fourth day. N.R. again after 18, 21, 24, 27, 30, 30 gr. Q. (total 9·7 grm.). Took 10 gr. b.i.d. for one month, 5 gr. b.i.d.

for hree months, and then 5 gr. daily. N.R. maintained fourteen months, able to do more than when treated with digitalis.

Normal rhythm restored but not maintained. Cases XLIV–L.

A. *Rheumatic cases.*

Case XLIV, F., aged 23. Breathless three years. Heart moderately enlarged, mitral stenosis, and aortic incompetence. Slight failure. A.F. (EC.).

N.R. after 5, 10, 15, 20, 15 gr. Q. on successive days (total 4·2 grm.); maintained for four years on 5 gr. Q. b.i.d. in good health. Symptoms then returned. A.F. (EC.).

N.R. after 5, 10, 15, 20, 10 gr. Q. on successive days (total 3·9 grm.). Then 5 gr. t.i.d., but A.F. returned after five weeks. One year later with digitalis unable to do as much as with restored N.R.

Case XLV, M., aged 29. Two years breathless and unable to work, N.R. (EC.). Two weeks worse. Heart slightly enlarged, mitral stenosis and aortic incompetence, slight failure. A.F. (EC.).

N.R. after 5, 10, 15, 20, 10 gr. Q. on successive days (total 3·9 grm.). Took 5 gr. b.i.d. for sixteen months and continued in fair health with N.R. Failed to continue Q. when transferred elsewhere. A.F. and symptoms returned after four months. After two years heart much enlarged, slight failure; on digitalis.

Case XLVI, F., aged 56. Twice in three years palpitation for twelve hours. One month continued breathlessness. Heart slightly enlarged, mitral stenosis, some oedema. B.P. 140/95. A.F. (EC.).

N.R. after 5, 10, 15, 20 gr. Q. on successive days (total 3·3 grm.) Took 5 gr. t.i.d. for three months and b.i.d. for one year. N.R. with freedom from symptoms maintained for thirty-one months. A.F. returned, treated with digitalis elsewhere. Two months later emboli of leg and spleen; in fair health after six months (May 1927).

Case XLVII, M., aged 22. Short of breath eight years. At work till two weeks ago. Heart slightly enlarged, mitral stenosis and aortic incompetence, no failure. A.F. (EC.).

N.R. after 5, 10, 5 gr. Q. on successive days (total 1·3 grm.); maintained after one year on 5 gr. b.i.d.; felt well. Q. then stopped elsewhere, fibrillation returned after four months.

Auricular flutter with 2 : 1 and 3 : 1 block after 5, 10, 15, 20, 15 gr. Q. on successive days (total 4·6 grm.); after two more days with 15 gr. Q. stopped because of three short attacks of 1:1 flutter. A.F. returned a month later, doing light work after two years, but ten months later embolism of anterior tibial artery.

Case XLVIII, M., aged 35. R.F. at 10 years. No work for three years. Heart slightly enlarged, mitral stenosis, some oedema. A.F. (EC.).

A.F. persisted after 5, 10, 15, 20, 25, 30, 30, 30, 30, 30, 35, 40 gr. Q. on successive days (total 19·8 grm.). Digitalis again, then N.R. after 10, 20, 30, 15 gr. Q. on successive days (total 4·9 grm.). Failed to take Q. after a month. A.F. returned after eight months. Fairly well, with digitalis a year later (May 1925).

B. *Thyroid cases.*

Case XLIX, F., aged 50. Small thyroid cyst, no hyperthyroidism. Two years dyspnoea. Heart slightly enlarged, no failure. B.P. 150/90. A.F. (EC.).

N.R. after 3, 9, 12, 15, 18, 18 gr. Q. on successive days (total 5·5 grm.). Took 5 gr. t.i.d. for one month only. N.R. maintained three months. Nine months later, satisfactory with digitalis.

Case L, F., aged 55. Firm goitre for twenty years, no hyperthyroidism. Two years attacks of palpitation for a few hours. Four months breathless, five days much worse. Heart slightly enlarged, no failure. A.F. (EC.).

N.R. after 2½, 5 gr. Q. on successive days, i.e. on eighth day of A.F. (total 0·5 grm.). Took 5 gr. daily. Then partial thyroidectomy; during next four months, one, three, one, and one attacks of a few hours. Possibly Q. only stopped one paroxysm of unusual length; more likely it stopped A.F. which had become established. As paroxysms still occurred, included as case with relapse.

Normal rhythm not restored. Cases LI–LXIV.

A. *Rheumatic cases.*

Case LI, F., aged 28. R.F. at 7 years. In hospital with A.F. one year ago. Heart considerably enlarged, mitral stenosis and aortic incompetence, general failure. A.F. (EC.).

After 5, 10, 15, 20, 25, 10 gr. Q. on successive days (total 5·5 grm.) pulse regular, flutter with 2 : 1 block (auricle 276). Much worse with haemoptysis. 5 gr. Q. t.i.d. continued four days with no change. Dramatic relief with digitalis; A.F. returned third day (EC.). Satisfactory progress eight months later.

Case LII, M. aged 28. Four months cough and dyspnoea. Heart enlarged, mitral stenosis, moderate failure. A.F. (EC.).

After 5, 10, 15, 20, 25, 30 gr. Q. on successive days (total 6·8 grm) A.F. persisted. Digitalis satisfactory, but six weeks later right leg numb up to knee. Amputation advised but not performed, clot palpable in femoral artery; patient died, no necropsy.

Case LIII, M., aged 23. Rheumatism at 16 years. Ten months breathlessness and palpitation. Heart moderately enlarged, mitral stenosis, slight failure. A.F. (EC.).

After 5, 10, 15, 15, and 15 gr. Q. on successive days (total 3·9 grm.) stopped for palpitation. Satisfactory with digitalis for eighteen months when failure increased: death one year later.

Case LIV, F., aged 16. R.F. at 15, in bed for six months. Palpitation and breathlessness, pulse irregular five months later. Heart moderately enlarged, mitral stenosis, slight oedema of feet. Rheumatic nodules. A.F. (EC.).

After 5 and 10 gr. Q. on successive days (total 1·0 grm.) rigor with vomiting, collapse, and increase of congestive failure. Q. stopped, digitalis given two days later, but still got worse. Second day after digitalis, regular tachycardia (? flutter at rate 240–60 with 2 : 1 block); died ten days later, no necropsy.

Case LV, M., aged 49. One year breathless and unable to work. Heart not enlarged, mitral stenosis, no failure. A.F. (EC.).

After 5, 10, 15, 20, 25, 30, 35 gr. Q. on successive days (total 9·0 grm.) stopped because of rapid ventricular rate. Digitalis treatment satisfactory for one year, then failure and death.

Case LVI, M., aged 39. One year breathless. Heart slightly enlarged, mitral stenosis, no failure. A.F. (EC.).

A.F. persisted after 5, 10, 15, 20, 25, 30 gr. Q. on successive days (total 6·8 grm.). Satisfactory progress with digitalis three years later.

Case LVII, F., aged 27. One year breathlessness with cough and palpitation. Heart moderately enlarged, mitral stenosis, slight failure. A.F. (EC.).

After 5, 10, 15, 20 gr. Q. on successive days (total 3·2 grm.) A.F. persisted. Ventricular rate increased to 160; vomiting with palpitation and collapse.

Symptoms started before Q., but aggravated by it; associated swelling of the hands may have been exacerbation of rheumatic infection. Satisfactory with digitalis ten months later,

Case LVIII, M., aged 25. Rheumatism at 13 years. Five months cough and breathlessness. Heart moderately enlarged, mitral stenosis and aortic incompetence, some oedema. A.F. (EC.).

After 5, 10, 15, 20, 25, 30, and 30 gr. Q. on successive days (total 8·8 grm.) discontinued for nausea. Later flutter with 2 : 1 block (auricle 240–300) developed after 10, 20, 30, 30 gr. Q. on successive days (total 5·9 grm.). Pulse regular seven days, but ventricular rate increased from 110 to 160. A.F. returned third day of digitalis; satisfactory progress ten months later.

Case LIX, F., aged 31. R.F. at 5 years. Two years severe dyspnoea. Heart considerably enlarged, mitral stenosis, moderate congestive failure. A.F. (EC.).

After 5, 10, 15, 0, 0, 0, 20, 25, 25, 25, 0, 0, 0, 25, 30, 35, 40, 45 gr. Q. on successive days (total 20·4 grm.) A.F. persisted. Improved with digitalis; fair health one year later.

Case LX, F., aged 64. Chorea at 16 years. One year ago in hospital with failure. Progress fairly satisfactory with digitalis. Heart slightly enlarged, congestive failure. B.P. 145 (approx.). A.F. (EC.).

After 5, 10, 15, 20, 25, 25, 25, 30 gr. Q. on successive days (total 10·0 grm.) A.F. persisted. With digitalis fairly satisfactory for six months, but then increasing failure again.

B. *Thyroid cases.*

Case LXI, M., aged 58. Thyroid enlarged for forty years; no hyperthyroidism. Four months breathlessness and palpitation. Heart slightly enlarged, no failure. B.P. 180/115 (approx.). A.F. (EC.).

Q. started ten days after hemithyroidectomy. Pulse regular after 5, 5, 10 gr. Q. on successive days (total 1·3 grm.). Continued 5 gr. b.i.d. with pulse sometimes regular, sometimes irregular—probably flutter with 2 : 1 block. This persisted in spite of Q. 10 gr. t.i.d. Digitalis induced 4 : 1 block (auricle 240–280) (EC.). Still able to follow light occupation, one year later, but flutter persisted (January 1928).

C. *Other cases.*

Case LXII, M., aged 57. Four months breathlessness. Heart slightly enlarged, no failure. Pulse regular, 40. B.P. 130 (approx.). W.R. negative. A.F. with complete heart-block (EC.).

N.R. with complete heart-block after 5, 10, 15, 20, 25 gr. Q. on successive days (total 4·9 grm.). 30 gr. Q. continued for five days; on second day increasing ventricular rate (80) and later auricular flutter (rate 240). On fifth day rash, and two hours later cyanosis, then unconscious for ten minutes, Q. stopped; next day A.F. with complete block. Three years later, sedentary work, heart rhythm unchanged.

Case LXIII, F., aged 53. Seven years attacks of palpitation and dyspnoea. Three months continuously short of breath. Heart slightly enlarged, slight failure. A.F. (polygram).

Pulse regular, probably N.R., after 2½, 5, 10, 15, 20, 25, 25, 25, 25, 25 gr. Q. on successive days (total 10·8 grm.). Next day felt well, pulse regular, but oedema of the feet observed for the first time. Took 5 gr. Q. after breakfast and 5 gr. after lunch; in the afternoon sat up in bed and died instantaneously. No necropsy.

Case LXIV, M., aged 59. Two years breathlessness with oedema, digitalis intermittently. Heart much enlarged, moderate failure. B.P. 180 (approx.). A.F. (EC.).

Q. stopped after 5, 10, 15, 20, 25, 25, 30, 30, 30, 30, 35, 40 gr. on successive days (total 21·0 grm.). Improved on digitalis two weeks, then septic throat with bronchitis; died one month after last quinidine. At necropsy no valvular disease, much bronchitis, early hobnail liver, renal fibrosis.

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FEBRILE ALBUMINURIA, WITH SPECIAL REFERENCE TO PNEUMONIA[1]

By L. C. HILL

The significance and importance of the so-called febrile albuminuria of pneumonia and typhoid fever can only be demonstrated by a systematic routine examination of the urine such as was so characteristic a feature of the late Dr. J. W. Russell's clinical work. The fact that it had been his intention to make this the subject of his next investigation, had he lived, supplied the writer with the inspiration to carry out these investigations. Although the literature of the last thirty or forty years tends to place the albuminuria of pneumonia in the category of a febrile albuminuria, it may be possible, by a study of the urine of these twenty-one cases of pneumonia and three cases of typhoid fever, to draw some inferences and conclusions with regard to febrile albuminuria as a whole.

The cases have been collected, with one exception, from the medical wards of the General Hospital, Birmingham, and the Children's Hospital, Birmingham.

Estimation of Albumin in the Urine.

For the purpose of this study, it was essential that the method of estimation should be capable of rapid application, should be reasonably accurate, and should not be limited in its use either to a very small or, as in the case of Esbach's albuminometer, to large degrees of albumin in the urine. Extreme accuracy was, fortunately, not essential, and only a comparative value is claimed for the results obtained. Again, variations in brightness of the daylight tended to render impracticable any method not simple and rapid of application. It was the opportunities enjoyed by the writer of seeing such a method constantly in use, and the results obtained by the late Dr. J. W. Russell, which gave rise to a consideration of its possibilities in a study of febrile albuminuria. Indeed, it was the avowed intention of Dr. Russell to embark upon a study of pneumonic albuminuria, which he considered to be of constant occurrence and of little understood significance in pneumonia.

Russell's method. This has been adopted by the writer because it fulfils adequately the requirements of this study, which do not include perfect accuracy. It was never claimed by the inventor to have more than a comparative value, but, at the same time, in his hands it attained to a high degree of accuracy, (a degree certainly not approached in these investigations).

[1] Received June 4, 1928.

The method is modelled directly upon Gower's haemoglobinometer, save only that a fluid containing a standard haze is substituted for the tinted jelly. Briefly, a comparison is made between albumin precipitated in the urine and the standard haze, and the number of dilutions needed to match this standard is a measure of the amount of albumin present.

Special, flat-bottomed tubes, made of thin glass, measuring 15 cubic centimetres by 1·1 centimetres (internal bore) are used.

The standard haze is made from three stock solutions, and should be made up afresh for each day's estimations.

The three stock solutions consist of:

(i) A solution of N/500 barium chloride in distilled water (0·02443 per cent.);

(ii) a solution of N/500 magnesium sulphate in distilled water (0·02467);

(iii) pigmented, distilled water; the addition to every 100 c.c. of distilled water of 0·04 c.c. of a saturated solution of picric acid, and 0·02 c.c. of freshly made 0·2 per cent. bismarck brown together produces the appearance of pale urine.

A crystal of thymol should be added to each of solutions (i) and (ii). The bottles in which the standard solution of barium chloride and magnesium sulphate are kept should be thoroughly treated with hydrochloric acid before being used, as this has been found to delay, if not altogether abolish, a tendency for the haze produced by their interaction to diminish at the end of a fortnight.

The standard is produced by mixing together in one of the special standard tubes, previously thoroughly cleaned with distilled water, 0·5 c.c. of each of the stock solutions of barium chloride and magnesium sulphate, and then allowing the mixture to stand for five minutes; at the end of this time 10 c.c.[2] of pigmented water is added, and the haze is ready for use.

Dr. Russell preferred to make up his stock solutions afresh every month, and the writer has taken a similar precaution against possible inaccuracy.

In order to bring the haze of albumin in the urine to the same density as that of the standard haze, a varying amount of dilution will be necessary. This is carried out and regulated by means of a pipette graduated in cubic centimetres. The quantity of albuminous urine taken for dilution varies according to the amount of albumin present; for instance, it may be convenient to take anything from $\frac{1}{10}$ c.c. to 5 c.c. according to whether the amount of albumin present is 'a very faint haze' or a 'heavy cloud'. Indeed, if the precipitate of albumin comes down really heavily, it is advisable, from the point of view of time-saving, to make preliminary dilutions with water; the end result obtained is then, of course, multiplied by the number of these preliminary dilutions.

Again, it is highly desirable, if not absolutely necessary, to keep the fluids in the two tubes which are being compared at about the same level of pigmentation. To bring this about (and failure to do so is one of the main causes of

[2] When he described his method, Dr. Russell added only 5 c.c. of pigmented water, thus producing a heavier standard haze. Later, he gradually reduced the density of his standard, ultimately reaching a degree of fineness well below that used in this study.

inaccuracy) it may be necessary to dilute either with plain or with pigmented water, and, sometimes, when the urine to be examined is paler than the standard haze, it may even be advisable to add a drop of bismarck brown to the urine.

Precipitation of the albumin in the urine can be produced by more than one means, but not all the methods ensure the complete precipitation which is so essential. For small quantities of albumin, heat and the addition of acetic acid is reliable, but with any high degree of albuminuria, complete precipitation cannot be relied upon by this method (33). The colour of picric acid renders it unsuitable for use in these circumstances. Salicyl sulphonic acid is a very reliable precipitant, but it needs to be used in excess in order to retain the precipitate in much dilution, and this involves an undesirable amount of dilution, while its colour increases the difficulty in obtaining a good match. Dr. Russell solved the difficulty by discovering that the substitution of a few drops of a saturated solution of salicyl sulphonic acid for acetic acid after boiling ensures a complete precipitation. The writer has used this method throughout these investigations, finding that three or four drops of salicyl sulphonic acid, added after boiling, will produce as complete a precipitation of albumin in one quarter of a test-tube full of urine as would need half a cubic centimetre of the acid added in the cold.

Turbidity of the urine is occasionally a source of difficulty and delay, and, lately, it has seemed advisable to subject each specimen, whether clear or turbid, to a rigorous filtration—a thickness of even half a dozen filter-papers being occasionally called for in the case of a particularly turbid urine. This has been the cause of great delay. When the turbidity has been due to a heavy bacilluria, such means of combating it have been mainly ineffective and the accuracy of the result has been definitely affected adversely. This has been, fortunately, of rare occurrence.

In order to measure the hazes obtained, it is necessary to give to the standard haze a unit value, which has been called a unit of albumin and the charts included are all expressed in units of albumin.

A very great obstacle to accuracy lies in the necessity for working in daylight which varies from day to day in its quality. Much of the inaccuracy of the readings has its origin in the light of a dull day. And it is not expedient to put off an examination until the morrow, as turbidity associated probably with some bacilluria has by that time ruined any hope of an accurate result.

Of no less importance is the dark background against which to match the hazes. A combination of good light and a dark background will throw into view a haze which is invisible under any other conditions.

The absolute value of the unit the writer does not know. Dr. Russell placed it somewhere low down in the third place of decimals of a gramme per 100 c.c. Some idea of its relative delicacy can be realized when remembering that nothing less than 0·1 grm. per 100 c.c. is measurable by Esbach's method. With regard to the accuracy of the method as a whole, Russell's own words are 'I do not claim that all my results reach this degree of accuracy.' 'Dark

days, hurried work, and personal conditions all have their effect. But that this method is capable of giving a reasonably reliable picture of the variations in the output of albumin in a given case, I have but little doubt.'

Pneumonic Albuminuria.

The presence of albumin in the urine in pneumonia was first described, according to Edmund Parkes, by Solon, who found it present in only two out of twenty-four cases in a particular series. He made the mistake of connecting it with the stage of convalescence. Other contributors to the literature whose figures vary widely include Frankel and Reiche 42·6 per cent., Rosenstein 23·1 per cent., Craemer 68·18 per cent., Stoertz 52·1 per cent., Bleuler 52 per cent., Morhart 37 per cent., Pohlmann 37 per cent., and Petzold 14 per cent., mentioned by Osler (10), Finger (Vienna) 45 per cent., Becquerel (Paris) 42·8 per cent., mentioned by Edmund Parkes (16). Other statistics collected by Howship Dickinson (7) include Wilson Fox 31 per cent., Griesinger 52 per cent., Martin, Solon, and Ziemsson 8·3 per cent., and Metzgan, who failed to find it once in forty-eight cases of pneumonia. Dickinson seems to have been convinced that all these percentages were on the low side, and suggests that if a sufficiently careful examination be made, albumin will be found in every case of pneumonia. He quotes, in support of this, the results of an investigation by Izambard Owen, who not only found albuminuria in twenty-two out of twenty-six cases of pneumonia, but even suggested that a more frequent examination of the urine between the second and tenth days would probably have led to its discovery.

Herr Weber (12), at the Greifswald Medical Clinic, found albumin, casts, and cells present in the urine of every one of nine cases of pneumonia.

During the whole time in which this subject has been of particular interest to the writer, in not one single instance has the urine of a patient suffering from lobar pneumonia or primary broncho-pneumonia failed to show the presence of albumin at some stage in the illness.

The method used by the writer in these investigations is exceedingly delicate, but by no means the least important item in its use is the inspection in a good light against a dark background. Again, since in many cases it is only a very minute haze of albumin which is present, routine filtering of the urine and the use of clean test-tubes is highly advisable.

The occurrence of albuminuria at the height of the disease, even before signs of pulmonary consolidation become evident, completely refutes the old theory propounded by Solon and others of the early observers that pneumonic albuminuria is due to the passage out of the circulation of exudate absorbed from the resolving lungs. That it is due to the implication of the kidneys in a general toxaemia or septicaemia, the most marked local seat of which is the lungs, can hardly now be gainsaid.

According to Lord, Frankel and Reiche (31) found pathological changes in the kidneys in all but one of forty-five fatal cases of pneumonia. These changes

were present in the renal epithelium and consisted mainly of plasmolysis and coagulation necrosis, without any evidence of small cell infiltration. In a few instances interstitial and vascular changes resembling that found in chronic nephritis were present, but it must not be forgotten that cases of chronic nephritis frequently end up with a terminal pneumonia, and so such statistics must be accepted with due reserve.

The writer's own experience has been limited to the investigation of only two cases in the post-mortem room, neither of which had a history of any previous renal disease, and both of which were under the age when pathological changes usually occur in the vessel-walls. One was a young man of 20 years, while the other was a girl of 14 years. In the main the findings agree with those of Frankel and Reiche and of Osler. The condition of the kidneys in the two cases was similar. The organs were pale and increased in weight. The capsule appeared to be normal, and stripped easily, leaving a smooth surface, upon which the veins were seen to be engorged. Cut sections showed the cortex to be increased slightly in thickness, while the pyramids were evidently particularly congested. Microscopical examination showed all degrees from cloudy swelling, vacuolation and desquamation of the epithelial cells lining the convoluted tubules, to fatty degeneration and, here and there, actual areas of necrosis. There was also some cloudy swelling of the cells of the glomeruli, with albuminous exudation into the lumen of Bowmann's capsule, but they were affected less than the convoluted tubules. The loops of Heule and the collecting tubules did not appear to be damaged. The venules were generally engorged, but the arteries showed little change. There was no sign of any small cell infiltration whatever.

In the opinion of the writer, there occurs, in such cases as are uncomplicated by old venal lesions, definite changes in the renal tissue, of a degenerative rather than an inflammatory nature. The degree of degeneration depends, no doubt, upon the severity of the bacterial toxaemia or septicaemia, and it is probable that, in the milder cases, in which the general condition is good and the albuminuria slight, the upset of the renal epithelium is nothing more than a transitory cloudy swelling sufficient to hamper its selective action in forbidding egress to the plasma proteins.

Description and Discussion of Results.

While it is upon the albuminuria present in pneumonia rather than pneumonic 'febrile' changes in the urine as a whole that attention has been mainly focused in this study, at the same time an effort has been made to record the presence of casts, blood-cells, renal epithelium, and other evidence of renal involvement. Attention has centred mainly upon the albuminuria, its variations at the different stages of the pneumonic process, and in the different types of pneumonia. In order to throw some light upon the justification for the use of the epithet 'febrile' in describing pneumonic or typhoidal albuminuria, the estimations of albumin day by day have been graphically recorded in units of

albumin and compared upon charts with the temperature present at the time. It has not always been possible to follow out a case methodically day by day. On the charts can be seen the degree of albuminuria at the different stages, the length of time during which it is present, any persistence after the temperature has finally settled, its presence or not on discharge from hospital and, in a few cases, where this has been possible, its presence in the Out-patient Department afterwards. In a few cases, too, the effect of the orthostatic position upon the disappearing albuminuria in convalescence, or the urine now free from albumin, has been observed and noted.

The intention was, at the beginning, to obtain a record of the daily output of urine in each case, but it soon became clear that this, particularly in the case of young children, was impracticable. More than two-thirds of the writer's cases have been obtained from the medical wards of the Children's Hospital, Birmingham.

As often as possible, the estimations have been made from 24-hourly specimens of urine or, at least (for here again the difficulty mentioned above arises), from a sample of the collected urine passed at intervals during the twenty-four hours; twenty-one cases of pneumonia have been followed out and no effort has been made by the writer to select any particular variety.

No one particular type of pneumonia has been chosen; examples of lobar pneumonia, primary and secondary broncho-pneumonia, and unresolved pneumonia are among the twenty-one cases. The difficulty of distinguishing satisfactorily between the different types of pneumonia arises most acutely in the case of children, for authorities differ widely as to the relative frequency of broncho-pneumonia and lobar pneumonia in childhood. Clinically, it cannot be disputed that attacks of pneumonia in children may, in their mode of onset, course, termination, and in their physical signs, closely resemble the lobar pneumonia of adults. Hence it must be understood that the writer has no intention of dogmatizing over the diagnosis in each individual case of pneumonia. Where, over the age of infancy, the case has been clinically one resembling a lobar pneumonia—where the onset has been sudden and unassociated with bronchitis, influenza, or any other condition, where the physical signs have been those of consolidation without accompanying moist bronchitic sounds, and where the termination has occurred by crisis—it has been included under the heading of lobar pneumonia. That the number of cases of secondary broncho-pneumonia has not been much larger may be due to the fact that the more serious types complicating measles and whooping cough cannot be admitted to the Children's Hospital.

It has been observed that while the relatively heavy albuminuria present at the height of the fever was apparently always associated with a more or less diminished output of urine, this output—in the few cases in which it was possible to obtain an even approximate record—increased only moderately after the crisis. So that, whatever increase may have occurred, it was certainly not proportionate to the massive diminution in the albuminuria which is so striking a feature of pneumonic urinary changes at the crisis.

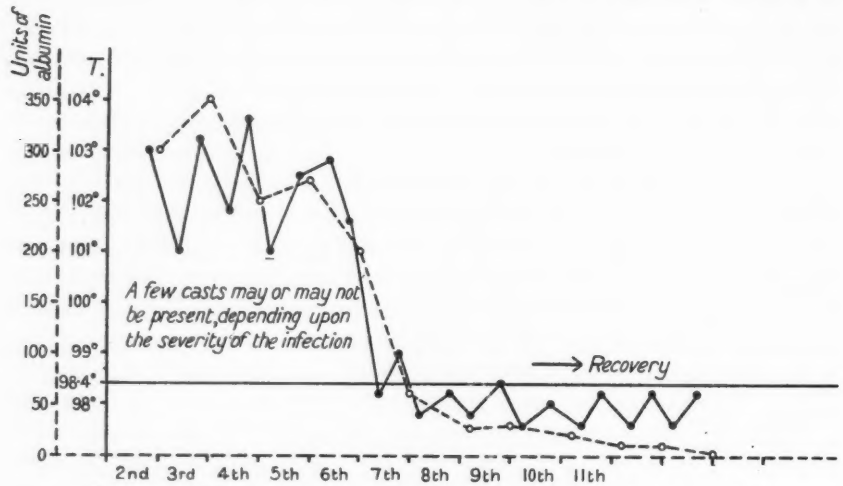
Albumin was present in the urine of each of the twenty-one cases of pneumonia and the three cases of enteric fever. This very strongly supports the contentions of Howship Dickinson and Izambard Owen, and, later, that of Russell. In each of the twenty-four cases (with the exception of those which ended fatally) the albuminuria persisted not only throughout the pyrexial period but also for a variable number of days afterwards, though in greatly diminished quantity. This residual trace was frequently so minute that it would be missed quite easily by a casual observer, unless precautions were taken to examine for its presence under favourable conditions.

Although variations in the albumin-content of the urine occur in the different types of pneumonia and in different stages of similar types, yet, on the whole, a fairly constant picture can be obtained from a study of these few cases. In a typical case of pneumonia, whether of the lobar or primary broncho-pneumonic type, the albuminuria reaches its maximum and remains high during the period of continued fever, falls suddenly and quickly to very small proportions at or around the crisis, while a trace persists for a variable number of days afterwards. The maximum has varied between 100 units (a light cloud) and 900 units (a heavy deposit) the larger quantities often being associated with the presence of pus cells, leucocytes, and casts. The explanation of those cases in which patients have gone out of hospital with a trace of albumin still present in the urine lies probably in their having been admitted during a 'rush' period and, in consequence, owing to the urgent call for beds, have had to be discharged prematurely to complete their convalescence in bed at home. In not one single instance has albuminuria been found in the Out-patients' Department a fortnight or three weeks afterwards.

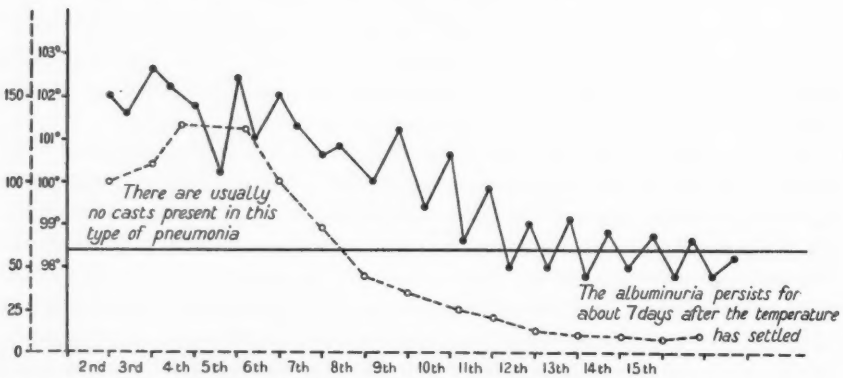
With regard to the effect of complications, the high swinging temperature due to the empyaema in two cases seems to have had little effect in bringing about any increase in the albuminuria, despite the fact that in one of these cases the urinary output was definitely diminished during the pyrexial period. What has been said of lobar pneumonia and primary broncho-pneumonia holds good, in a modified form, in the case of secondary broncho-pneumonia. In all but one of the five cases of this type included, the maximum albuminuria was very much smaller than that found in the other two varieties, and the fall occurred more slowly and gradually; the same tendency, however, for a trace of albumin to remain in the urine after the temperature had settled, existed. Two composite charts have been drawn up (Figs. 1 and 2) with the object of endeavouring to depict the typical excursion of the albuminuria in lobar and primary (pneumococcal) broncho-pneumonia on the one hand, and secondary broncho-pneumonia, on the other.

In addition to albumin, other morphological substances were found in the urines of some of the cases. In no less than seven of the twenty-one cases of pneumonia, casts of one kind or another were observed; and in five out of these seven they were very numerous and of the epithelial or granular varieties. Only in one case were red blood corpuscles discovered. A pure growth of the pneumo-

coccus of Frankel was obtained on sloped tubes of blood-smeared agar, in three out of twelve cases in which the attempt was made to culture from the urine. So that the following figures emerge from the findings in this study of the urine



COMPOSITE CHART I. Lobar pneumonia and primary broncho-pneumonia.



COMPOSITE CHART II. Secondary broncho-pneumonia.

of twenty-one cases of pneumonia, indicating the frequency of occurrence of the different pathological constituents

(i) *Albumin*, in 21 out of 21 cases, or 100 per cent.
(ii) *Casts*, of any kind in 7 out of 21 cases, or 33·3 per cent.
„ (excluding hyaline) in 5 out of 21, or 23·8 per cent.
(iii) *Red blood corpuscles* in 1 out of 21, or 4·8 per cent.
(iv) *Pneumococci* were grown in 3 out of 12, or 25 per cent.

In three of the four fatal cases, not only was the albuminuria strikingly heavy throughout, and definitely and progressively on the increase shortly

before death—a phenomenon already noted by Russell—but, in addition, epithelial, granular, and hyaline casts were present in abundance, while a pure growth of the pneumococcus was obtained from the urine in the only two cases in which it was attempted. So that it would seem that the intensity of the albuminuria, the presence of casts, and the presence of pneumococci in the urine all have an influence upon the prognosis. The urine of the fourth case, in which the albumin-content remained low throughout, contained no casts. It was that of a young man who died, apparently prematurely, from sudden heart failure following uncontrollable restlessness and intractable insomnia.

The proportion of globulin to albumin was estimated, somewhat roughly, in four of the cases by adding acetic acid to the urine in the cold, and comparing the haze produced with the total albuminuria. In each instance the albumin was found to be forming by far the greater part of the coagulum—the actual ratios ranging from 4 : 1 to 9 : 1 = albumin : globulin. This is interesting in view of the findings of R. L. Mackenzie Wallis (34) who, in a paper on 'Non-nephritic Albuminurias', compiled a table of the average ratio of albumin to globulin encountered in the different varieties of albuminuria. The following is a copy of his table:

Functional albuminuria,	albumin 2, globulin 1.
Leaky kidney,	albumin 1, globulin 2.
Chronic nephritis,	albumin 6, globulin 1.
Toxic nephritis,	albumin 6, globulin 1.

From this aspect, at least, pneumonic albuminuria does not appear to fall into line with the non-nephritic, functional albuminurias. At the same time, too much importance should not be attached to this aspect of the case, for observers in the past have been unable to arrive at anything like definite conclusions with regard to this ratio in the different types of nephritis.

One other point of interest accruing from the study of these cases was the presence, in three instances, of an orthostatic reaction during convalescence. In only a few of the cases was it possible to obtain the ideal conditions of five to ten minutes of standing in the position of slight lordosis. The patients' weakness and, in this collection of cases, the tender years of many of them did not justify their being subjected to such strain. In view of the presence of an orthostatic reaction in the albuminuria of some cases of established mild nephritis, a fact which has been recognized by Bass (4) in his 'Review', and by Russell (6), pneumonic albuminuria cannot now be included among the functional varieties of which orthostatic albuminuria was thought to be a member.

With regard to the three cases of enteric fever, no valuable conclusions can be drawn from such scanty material. The urine of each of the three children contained both albumin and formed elements in the deposit. The albuminuria was, in two of the cases, exceedingly heavy, and there were numerous casts of all kinds; in one of them there was a profound haematuria which lasted for

three weeks and made an accurate estimation of the albuminuria impossible. As in the cases of pneumonia, but for a very much longer period, a trace of albumin persisted for some time after the temperature had settled.

The unusual acidity of the urine in many of the cases investigated cannot be ignored as a possible factor in the causation of febrile albuminuria, especially in the light of recent work by Osman, on 'The Prophylactic Effect of Alkaline Therapy upon Scarlatinal Nephritis and Albuminuria'. He claimed to have reduced the occurrence of nephritis in scarlet fever from 4 per cent. to $1\frac{1}{3}$ per cent., by the administration of potassium citrate and sodium bicarbonate in a quantity sufficient to maintain the urine in a neutral state from admission until discharge. Together with Dr. Colwill, of Manchester, in a series of cases of scarlet fever, he separated an 'A' group, in which the urine was acid (to phenolphthalein), from a 'B' group, in which it was alkaline. Whereas 67 per cent. of the 'A' group developed either nephritis or albuminuria, only 3·4 per cent. of the much larger 'B' group showed this complication.

While the contributors to the literature of the subject have shown a very considerable diversity of opinion upon the frequency of albuminuria in pneumonia, they are at one in pronouncing the rarity of acute nephritis. Apart from a few who refrain from committing themselves, on the plea that it is quite impossible to distinguish between a mild nephritis and a severe febrile albuminuria, the remainder place the frequency of this complication at between 1 and 2 per cent. As far as can be ascertained, oedema is unknown, and persistent renal disease has virtually never been traced to this origin. We are, therefore, forced to assume that, if a line of demarcation is to be drawn, from the clinical point of view, the presence of blood or casts (other than hyaline) or both, constitute nephritis. If this is correct, then nephritis must be very much more common in pneumonia than is generally believed, and it must be of a transitory and mild type. According to this ruling, out of twenty-one cases of pneumonia of all types, five (or 23·8 per cent.) were accompanied by evidence of renal affection sufficient to justify the diagnosis of mild nephritis. These five cases were all very severe from the clinical point of view. No less than three terminated fatally, and one of the other two developed a pneumococcal septicaemia and showed a trace of albumin in his urine for three weeks after the temperature had settled. Pneumococci were grown from the urines of three out of the four cases in which it was attempted. The albuminuria in each of the five cases was noticeably heavy, but not greatly in excess of that present in some of the urines of milder cases in which casts and pneumococci apparently were not found. On the whole, therefore, the writer prefers to view the question from the same standpoint as Senator and Aufrecht, and considers that it is simply a matter of degree. The more severe the attack of pneumonia, the greater is the assault upon, and the consequent damage to, the kidneys.

The percentage of cases in which the pneumococcus was cultured from the urine, taken in conjunction with Frankel's and Reiche's work in the post-mortem room—which has been mentioned more fully elsewhere—leave little room for

doubt that this assault is not infrequently bacterial rather than toxic, and then usually pneumococcal.

It is only when the subject is viewed from the standpoint of the pathology that it becomes possible to appreciate the differences in the degree of involvement of the kidneys and the fundamental features which distinguish the toxaemic kidney, as we will call it, from the pathological conditions found in true nephritis.

In the milder cases, the assault may be hardly capable of causing more than a transitory cloudy swelling of the epithelium of the glomerular tufts with albuminous exudate into the capsular lumen, associated with a cloudy swelling of the cells lining the convoluted tubules, a degree of damage sufficient to interfere temporarily with the selective action of the cells in preventing the escape of the proteins of the blood-plasma. The renal recovery in such cases is at first rapid, being coincident with the return to a normal condition of the urine immediately after the crisis. The cells, however, are not completely regenerated for about a week afterwards. The high degree of concentration, the scanty output, and the diminished excretion of chlorides which are so constant a feature of pneumonic urine during the febrile period, disappear at the crisis, but the increased uric acid content usually continues for a few more days, and opinions still differ as to whether this is due to the disintegration of the exudate in the alveoli or to the leucocytosis. In any case, the carbon dioxide content of the plasma does not indicate any degree of acidity.

In the more severe cases, it is probable that the main force of the attack is delivered against the epithelium lining the convoluted tubules, the cells of which show cloudy swelling, vacuolation, and desquamation, with, possibly, secondary fatty or other degenerative and necrotic changes; this, in its turn, leads to the shedding of the degenerated cells into the lumen and the ultimate appearance in the urine of epithelial and granular casts. The venules are congested and there may be here and there thrombosis with extravasation of blood, but usually the arteries and arterioles show little significant change, and there is virtually no small cell infiltration. Thus the degenerative, rather than the inflammatory lesions present, which are capable nevertheless of complete recovery, are the distinctive features of the pathology of the so-called febrile kidney.

Conclusions.

1. Albumin is present, in considerable quantity, in the urine of every case of pneumonia, at some time during its course.

2. The presence in the urine of a haze of albumin may be of diagnostic value in a doubtful case.

3. The degree of albuminuria corresponds broadly with the height of the temperature in pneumonia, but differs in its tendency to persist in small quantities for some time after the temperature has settled.

4. No correspondence exists between the albuminuria and the temperature during the course of such complications as empyaema or mastoid suppuration.

5. Although the curves indicating the quantity of urine secreted and the degree of albuminuria tend to be inverse in their ratio, there is no definite relationship between them.

6. The intensity of the albuminuria is, on the whole, proportional to the severity of the case, and so has a decided bearing upon the prognosis.

7. Casts accompany the albumin in a considerably greater proportion of cases of pneumonia than is generally believed, and, indicating an unusually severe attack, also have a bearing upon prognosis.

8. An increase in the intensity of the albuminuria occurs shortly before death in the majority of fatal cases of pneumonia.

9. The raised temperature is not in itself the cause of the albuminuria. From this and other circumstances, it is probable that febrile albuminuria, in the true sense of the word, does not exist, but that some degree of renal damage is always present. The word febrile should therefore be dropped, because, while there are febrile conditions in which albuminuria may be absent (such as malaria, chronic tuberculosis, heat-stroke, and influenza), there are often present, in addition to the albumin, morphological elements which postulate a definite glomerulo-tubular lesion.

10. The distinctive feature of the histological picture of the kidney in febrile albuminuria is the absence of tissue reaction of an inflammatory nature, and the presence of tissue changes which are certainly degenerative.

The writer wishes to express his gratitude to the Honorary Physicians on the Staff of the General Hospital and the Children's Hospital, Birmingham, in particular to Dr. Parsons, Dr. Ball, Dr. Wilkinson, Dr. Smellie, and Dr. Braid, for the kind permission, always readily given, to make use of cases occupying their beds; to Dr. Hillier for his advice and assistance in the preparation of the solutions; and to the sisters and nurses in the medical wards of both hospitals for the trouble taken, among many, day after day, to procure 24-hourly specimens of urine—in many cases from infants under one year of age.

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TABLE OF

Case.	Patient's Name.	Age.	Where Observed.	Result.	Maximum Temperature.	Maximum Albuminuria.	Red Blood Corpuscles.
							Lobar
		Yrs.				Units.	
I	Bedwell, Florence	30	General Hospital, B'ham	Recovery	104 F.	350	0
VII	Haynes, Ernest	22	„ „ „	„	103·8	225	0
V	Garratt, William	21	„ „ „	Death	101	100	0
VI	Wellings, Alfred	22	„ „ „	„	103·6	290	0
XXI	Bedford, Leonard	20	In private practice	Recovery	104	270	0
XII	Cleaver, Vera	8½	Children's Hospital, B'ham	„	102	200	0
XIV	Clarke, Betty	7½	„ „ „	„	103·5	180	0
XVIII	Terry, Donald	4	„ „ „	„	104	210	0
XIII	New, Walter	4½	„ „ „	„	104	800	a few
							Primary
III	Quinsy, Henry R.	1 4/12	„ „ „	„	104·6	220	0
VIII	Harrison, Charles	2 8/12	„ „ „	Death	104	880	0
XI	Waring, Kenneth	4/12	„ „ „	„	101·8	310	0
XX	Adams, Norman	5½	„ „ „	Recovery	103·2	450	0
XIX	Smith, Alfred	4½	„ „ „	„	101·2	230	0
XVI	Bradbury, Barbara	6	„ „ „	„	104·2	150	0
							Secondary
II	Farrall, Joseph	3	„ „ „	„	102	40	0
IV	Copenstake, William	2 8/12	„ „ „	„	103·4	110	0
X	Pick, William	1	„ „ „	„	103	130	0
XV	Watson, Herbert	6	„ „ „	„	103	55	0
XVII	Penn, John E.	1	„ „ „	„	102·4	300	0
							Unresolved
IX	Moss, Leonard	1	„ „ „	„	101·4	90	0
							Enteric
XXII	Griffin, Beryl	6	„ „ „	„	101·4	100	0
XXIII	Griffin, Joan	9	„ „ „	„	104·2	370	0
XXIV	Flynn, Patrick	5	„ „ „	„	105	650	+ heavy haematuria

RESULTS.

Epithelial.	Casts Granular.	Hyaline.	Pneumococci Cultured.	Duration of Albuminuria beyond the Fever.	Albuminuria on Discharge.	Albuminuria after Discharge.	Orthostatic Reaction during Convalescence.
Pneumonia.							
0	0	a few	Not tried	5 days	0	None in Out-patient Dept. 14 days later	Yes. From 0 to 20 units after standing for 10 minutes
0	0	a few	„ „	5 days	0	Not tried	Not tested
0	0	0	„ „	—	—	—	—
many	many	a few	„ „	—	—	—	—
0	0	0	„ „	4 days	0	None after being up for a week	Negative
0	0	0	Negative	9 days	0	Not tried	Positive *
0	0	0	„	11 days	a trace	None in O. P. D. 14 days later	„ *
0	0	0	Not tried	3 days	0	Not tried	Not tested
many	many	many	Pure growth	3 weeks	a trace	None in O. P. D. 14 days later	Negative
Broncho-pneumonia.							
0	0	0	Not tested	6 days	0	„ „ „	„
many	many	many	Pure growth	—	—	—	—
a few	many	many	„	—	—	—	—
0	0	0	Negative	5 days	a trace	—	Not tested
0	0	0	„	7 days	0	None 14 days later	„ „
0	0	0	„	9 days	0	Not seen	Negative
Broncho-pneumonia.							
0	0	0	Not tried	5 days	0	None in O. P. D. later	„
0	0	0	„ „	5 days	0	Not seen	Not tested
0	0	0	Negative	8 days	0	„ „	„ „
0	0	0	„	5 days	a trace	None in O. P. D. later	Negative
0	a few	0	„	3 days	a minute trace	„ „ „	Not tested
Pneumonia.							
0	0	0	0	4 days	a trace	Not seen again	„ „
Fever.							
a few	a few	a few	—	3 weeks	0	„ „ „	Not tried
many	many	many	—	2 weeks	0	„ „ „	„ „
many	many	many	—	—	—	—	—

* In each case, the child stood in the bolt upright position for about 7 minutes in addition to being up out of bed for about 40 minutes.

CRITICAL REVIEW

SCHICK'S TEST AND ITS APPLICATIONS[1]

By SHELDON F. DUDLEY

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1. *Introduction.*

The Schick test deserves the notice of all medical men whatever their special line of practice, because, in many ways, it occupies a unique position in medicine. Schick's reaction is the only test for gauging the immunity of an individual to a common infectious disease, which is reliable, simple to perform, and, at the same time, so economical in time as to permit of its widespread

[1] Received November 30, 1928.

application to large samples of the population. The Dick test, owing to the difficulty of standardizing scarlet fever toxin, does not yet give the same feeling of confidence in the interpretation of Dick test records that the Schick test does. For these reasons a brief account of the development and applications of Schick's intracutaneous test for determining immunity to diphtheria should be of general interest.

After the classical work of Behring and his collaborators had proved that the blood of animals which had been inoculated with diphtheria toxin contained substances which could neutralize its harmful effects, Abel (1), in 1894, showed that the sera of certain human beings, when it was mixed with otherwise lethal doses of diphtheria toxin, could prevent the death of guinea-pigs. In other words, Abel had demonstrated that diphtheria antitoxin was often normally present in human blood. This observation was quickly followed by another. Fischl and Wunscheim (2) found that diphtheria antitoxin was present in 85 per cent. of the samples of blood from the umbilical cords of infants. Many other workers reported that the blood of many, but not all, people contained substances which could neutralize diphtheria toxin. Thus the existence of natural human diphtheria antitoxin in the circulating blood became a familiar concept.

In 1904 Marx (3), in order to economize in guinea-pigs, devised a new technique for standardizing therapeutic antitoxins. He mixed toxins of known potency with the antitoxin under examination and injected the mixture subcutaneously into the guinea-pigs. The potency of the antitoxin was then discovered by noting the minimum amount of antitoxin that was required to prevent a reaction in the experimental animal. Römer (4) in 1909 improved on Marx's technique by using very minute doses, and injecting the toxin-antitoxin mixtures into, instead of under, the skin of the guinea-pig. Römer's technique permits of a dozen or more tests being performed on the one animal. In 1910 Karasawa and Schick (5) using Römer's technique, but substituting human serum for that of immunized animals, confirmed the older observations of Abel and others, and showed, in addition, that while human diphtheria antitoxin was generally found in the blood of new-born infants, it disappeared as the age of the infant increased, only to reappear later. The disadvantages of Römer's method was that the test required a skilled immunologist and relatively a lot of time to perform efficiently. The test has the advantage of being an exact quantitative procedure whereby any quantity of diphtheria antitoxin in a serum from 0·001 of a unit per c.c. upwards can be measured precisely, and this makes Römer's procedure invaluable for accurately confirming certain conclusions formed from the study of Schick test results. In order to overcome the drawbacks of the Römer technique, in 1913 Schick and Michiels (6) transferred the whole procedure to the human subject. They injected a minute dose of diphtheria toxin into the skin and noted if any reaction occurred at the site of inoculation. If no redness appeared, the patient had enough diphtheria antitoxin circulating in his blood to neutralize the dose of injected toxin : he was

a Schick-negative, or immune, reactor. On the other hand, a red patch on the skin at the site of inoculation indicated that the injected dose of toxin had not been neutralized: the subject was a Schick-positive, or susceptible, reactor.

2. *The Technique and Interpretation of Schick Reactions.*

O'Brien (7) and his collaborators give a good account of the modern technique of the Schick test as practised in England. Suffice it to mention here that the conventional dose is 0·02 of a M.L.D. of a ripe diphtheria toxin contained in 0·2 c.c. of a suitable diluting medium. This dose and concentration of toxin has been found to give no specific reaction in the human skin when the blood-serum contains more than 1/40 to 1/20 of a unit of diphtheria antitoxin per c.c. When there is no antitoxin, or less than about 1/30 of a unit per c.c., in the blood of the tested subject, in about twenty-four hours, or earlier after the injection of a Schick dose of toxin a red, almost scarlet, patch about an inch in diameter appears, which is generally eliptical rather than circular; the major axis of the elipse being in the line of the limb. In four or five days the reaction, after first becoming more intense, begins to fade and desquamate, and becomes covered with bran-like flakes of cracked superficial epithelium which gives to the reaction a most characteristic appearance at the end of a week. The reaction disappears slowly, and remains evident for a month or more as a pigmented patch of variable tint. The uncomplicated Schick reaction has a well-defined edge and is not elevated above the surface of the surrounding skin. The above description covers at least three-quarters of the positive Schick reactions which are seen in those subjects who have not received any injections of a diphtheria prophylactic. In a minority of individuals, especially those who have been partly immunized, positive reactions are not so deep in colour or large in area, and they fade more quickly and may even stop short of desquamation. In exceptionally sensitive children the reaction may be the size of half a crown and proceed to actual vesiculation and superficial ulceration, which, however, invariably heals up quickly without any special treatment. Although in the majority of cases the Schick reaction can be read in twenty-four hours, all reactions should be checked and not finally recorded until the end of the week. O'Brien (7) states that in 21 out of 420 reactions (5 per cent.) the reading at twenty-four hours was doubtful; but most of these doubtful results became definitely negative or positive during the next five days. For practical administrative work in diphtheria prevention, the week-old reaction is invariably still evident, and therefore this is the time to record it. Even should it rarely happen that a transitory positive reaction appears and disappears within a week, for practical purposes the subject of such a reaction is immune, and his serum contains somewhere about 1/30 of a unit of antitoxin per c.c., which is the level of the titre of antitoxin above which the Schick reaction is inhibited.

The conventional Schick test dose of 1/50 of a M.L.D. was originated by Schick. Subsequent experience has gone to show that this quantity is the most

generally serviceable, and 1/50 of a M.L.D. has been the dose employed by practically all workers. Park (8), however, has lately increased the dose to 1/40 of a M.L.D., which seems to be unnecessary, and rather to be regretted, since Schick test statistics become less strictly comparable if the doses of toxin which have been used in any two contrasted series of tests are different. Presumably the strength of the Schick dose of toxin was raised in America in order to increase the margin of safety, and still further lower the chance of getting a negative Schick reaction in a subject who was not really immune to diphtheria.

Many writers on Schick technique have emphasized the importance of an exact dosage, and that great care must be taken to inject the toxin into, and not under, the skin. I tested this matter by giving sixty-three boys two injections of toxin at the same time. (*a*) The ordinary Schick dose of 1/50 M.L.D. in 0·2 c.c.; (*b*) one quarter of this dose, i. e. 1/200 of a M.L.D., in 0·05 c.c. There were thirty-five positive reactions to the ordinary dose, but only twenty-two of these also gave a reaction with the quarter-dose. With a further sample of sixty boys I repeated this experiment, using a half-dose (0·1 c.c.) instead of the quarter. This time the agreement was almost complete: only two boys failed to react to the half-dose out of thirty-four who reacted to the full Schick test dose. Therefore dosage is of importance, but should a few subjects in error get 0·25 or 0·15 c.c. instead of exactly 0·2 it probably would not cause any appreciable error in a series of ordinary tests. The other point that much stress is laid on was also investigated by the writer in a small series of parallel Schick tests done both subcutaneously and intracutaneously. It was found that no difference was made to the results, the subcutaneous positive tests were less definite and characteristic but still easy to interpret by a worker of any experience. Since this experiment was done, Haidvogl (9) has actually recommended subcutaneous, in preference to intracutaneous injection, on the ground that the results are just as reliable and easy to read, and less painful. Moreover, he says that pseudo-reactions are not evident when the test is performed subcutaneously. This investigation is only based on twenty-six tests, which seems scarcely a large enough sample on which to form such an opinion. I do not agree that subcutaneous tests are easier to interpret than intradermic, but that must be entirely a matter of practice and personal equation. Neither the intra- nor hypodermic injections cause appreciable pain. Thus, while it is wise to keep the dosage of injected toxin dilution as near to 0·2 c.c. as possible, exact dosage is not quite as important as some descriptions of Schick test technique lead one to believe, and if the injected fluid sometimes is given a little deep no difference at all will be made to the result. These points are of great practical importance because until the necessary practice and experience is gained, or if the syringe used is not absolutely tight, or the needle sharp, it is really not too easy to put *exactly* 0·2 c.c. into the superficial layer of the skin one hundred times in succession within half an hour. The above observations indicate that the Schick test technique has a good margin for error. This almost goes without saying, since no biological test,

which requires a meticulous accuracy in order to produce reliable results, ever becomes universally popular outside the laboratory. It also means that Schick reactions, even when done by inexperienced workers, can be relied on to give comparable results, *provided that the toxin itself is above suspicion.*

3. *The 'Delayed' Schick Reaction.*

The Schick-positive reaction generally appears within twenty-four hours, but for some unexplained reason a few reactions are not evident for a day or two after injection. This is one reason for reading or checking at the end of the week any reactions which have been interpreted during the first forty-eight hours as doubtful or negative. Dickenson (10), who has given attention to this type of Schick reaction, found a delay of over twenty-four hours in the appearance of 154 (14·1 per cent.) out of 1,091 positive tests. He saw six instances where the delay was over four days, and in one case no positive reaction was seen until five days, after the injection. When the delayed Schick reaction does appear it runs the usual course of the normal positive test.

4. *The Pseudo-Schick Reaction or Protein Reaction.*

The 'pseudo'-Schick reaction is not due to diphtheria toxin and can occur in either immune Schick-negative reactors or combined with the positive specific reaction to diphtheria toxin. This combined or pseudo- *and* positive reaction will be considered separately. The pseudo- *and* negative Schick reaction is, in most English samples, relatively about three times as common as the pseudo- and positive reaction. The pseudo-reaction is the chief cause of trouble in the interpretation of Schick tests, and because of it a control injection is usually considered essential in addition to the Schick test proper. Schick toxin is of course a broth filtrate in which diphtheria bacilli have been growing, it therefore contains many protein, and other, substances in addition to diphtheria toxin. Such foreign proteins are liable to produce a skin reaction in any one who is sensitized or in a state of *allergie* towards them.

In dilute solution, diphtheria toxin is very easily destroyed by heat, whereas the substances which are responsible for the pseudo-reaction are markedly thermostabile. Therefore a control injection is employed which has exactly the same composition as the test injection except that the control fluid has been heated to 80° C. for about fifteen minutes. It now becomes a simple matter to distinguish a pseudo- from a real Schick reaction. If there is any response at the site of the control injection it cannot be due to toxin, as that has been destroyed by heating; therefore any red mark on the control arm must be a pseudo- or protein reaction. There will of course be an exactly similar reaction at the site of the test injection, provided the tested subject is immune to diphtheria toxin; but if he also react to toxin, the protein reaction will be mixed up with the toxin reaction, in which case the test arm will not be exactly

similar to the control arm. The pseudo-reaction reaches its maximum in twenty-four to forty-eight hours and then subsides fairly rapidly, and is generally invisible by the end of a week. It is less intense and more 'blue' in colour than the specific reaction to diphtheria toxin. The ordinary pseudo-Schick reaction is accompanied by a slight superficial oedema, and is definitely raised above the surface of the surrounding skin. These characters make at least 80 per cent. of pseudo-reactions distinguishable from true Schick reactions at a glance by an experienced observer, even in the absence of a control injection. But there is no doubt that to gain this experience requires a little time. According to Dickenson (10) only 4·5 per cent. out of 222 pseudo-reactions were visible a week after injection, whereas true Schick reactions are practically always definite at the end of a week. This is the chief reason for recommending that all Schick reactions should be checked or read at the end of a week, by which time the majority of pseudos will have entirely disappeared, or will be so faint as to cause no trouble in interpreting the tests. Pseudo-reactions vary from a lesion at the site of injection, which appears to be little more than the trauma due to the needle, up to a rare condition which may well be termed a 'giant pseudo'. I (11) have only seen six cases of this condition, but Perry and Dickenson (12) have reported another one in a nasal carrier. At Greenwich these 'giant' protein reactions all occurred in cases who had had clinical diphtheria within six months of their Schick test. About twenty-four hours after injection the forearms to the extent of four to six inches round the site of the injections became red, tender, and oedematous. The temperature rose to about 100° F. These symptoms lasted for a day, and then the whole condition subsided within the next twenty-four hours.

Ordinary pseudo-reactions are found more frequently in this order among diphtheria convalescents, recently recovered cases, diphtheria carriers, and among the inhabitants of places where diphtheria is, or just has been, especially prevalent at the time of testing. For example, Dickenson (10) reports that out of 109 convalescent diphtheria patients 76 per cent. had positive Schick tests. Just after a big epidemic of diphtheria in 1921 in Greenwich Hospital School, 54 per cent. of fifty recovered diphtheria patients, 44 per cent. of sixty-two recently discovered diphtheria carriers, and 20 per cent. of the rest of the school, had protein reactions. At the same time I found only 8 per cent. of the new entries to the school had pseudo-Schick reactions, and Dickenson (10) only found 8·8 per cent. among 670 children who were under the age of 15, and who had not had diphtheria recently. Adults also, other things being equal, are more prone to be protein-sensitive than children. In Dickenson's series there were 19 per cent. of protein reactions among 431 subjects who were over 15 years of age. Again, workers have noted that the subjects with protein Schick reactions usually give marked local reactions when injected with diphtheria prophylactics, which are of course metabolic products of the diphtheria bacillus. Zoeller (13) found that a suspension of diphtheria bacilli, which had been heated to 105° C., when injected into the skin gave a reaction similar to a pseudo-Schick reaction

in the subjects of such reactions. He also showed that previous admixture with diphtheria antitoxin made no difference to the result, and that injections of the uninoculated broth, which was used for cultivating the diphtheria bacillus, or of horse serum, either produced no lesion of the skin, or one that was nothing like the pseudo-Schick reaction. All this evidence makes it pretty certain that the pseudo-Schick reaction is an allergic phenomenon, which indicates previous sensitization by the proteins of the diphtheria bacillus, as distinct from its specific toxin. The frequency distribution of pseudo-reactions, as given above, seems to increase with the probable intensity of the diphtherial contact and also to decrease with the interval between the time of the contact and the time of the test. Therefore a pseudo-reaction probably means, in most cases, a fairly recent contact with diphtheria bacilli. Some further observations also suggest that this is the case. Repeated Schick tests on the same group of boys showed that these Schick protein reactions can be gained and lost within six months or a year. A more striking piece of evidence which indicates that a pseudo-reaction means a recent, rather than a remote, diphtheria infection are the following figures: 841 boys tested in 1928 gave 16 per cent. of protein reactions. Seventy-nine boys in this series had a history of diphtheria while in the school. These recovered cases were only 20 per cent. pseudo-reactors; scarcely a significant difference from the general school population. However, if this sample was divided into thirty-one boys who had had clinical diphtheria within a year of being tested, and forty-eight who had had diphtheria more than a year before the performance of their Schick test, the first group contained 41 per cent. and the second only 8 per cent. of pseudo-Schick reactors. Thus the relative frequency of protein reactions was five times as great in the group known to have been recently infected by diphtheria bacilli as the frequency in the group who had not been infected, as far as was known, for over a year. As a rule, but not always, protein reactions are more frequent among negative than positive Schick reactors. This is because both the negative and pseudo-Schick reactions are probably caused by contact with diphtheria bacilli, hence in general it is found that the greater the number of immune Schick reactors in a community the greater the number of protein reactions. The frequency and intensity of pseudo-reactions must also to some extent depend on the brand of diphtheria toxin and the protein content of the test injections, and this has generally been the accepted explanation of the differences in statistics of pseudo-Schick reactions, such as the following examples show: In California (14), with only 45 per cent. of the population Schick immune, there were 19·3 per cent. of protein reactions. In New York according to Zingher (15), 67 per cent. of 60,000 individuals had negative Schick tests, and at the same time the percentage of pseudo-reactors was 14. Dickenson (10) gives 55 per cent. negative and 14 per cent. of pseudo-reactions in 1901 English subjects, but his sample was largely composed of the inmates of a fever hospital. The high susceptibility of the California population, combined with a larger number of protein sensitive people than usual, is rather exceptional, but the anomaly is capable of an

explanation that does not incriminate the broth filtrate, which was used for the Schick test in California, as being more prone to produce pseudo-reactions than that employed in New York or elsewhere. Protein reactions as previously indicated are much more common among people who have only recently become Schick immune, or recently been infected with diphtheria bacilli, than in Schick negative reactors of long standing. The Schick and anti-diphtheria campaign was undertaken because diphtheria had only recently become unduly prevalent in California. Therefore many of the Californians had not long had their negative Schick reactions, which implies that many had recently been in contact with diphtheria bacilli, and hence were more likely to be in a state *of allergie* towards diphtheria proteins than the inhabitants of such a city as New York, where diphtheria has been endemic for years. The study of the detailed statistics in the Californian report confirms this hypothesis. The percentage of protein reactions ranges from 2·6 to over 40 per cent. in different groups. Since the personal equation and toxin remained the same, some other explanation than that of a special brand of test material must be found to explain such discrepancies. In the body of the report the authors state: 'In Mendocino county, *where diphtheria had not been unduly prevalent*, the percentage of susceptibility was 80·1' . . . on consulting the tables at the end of the report it is discovered 'Mendocino rural' and 'Ukiah', the county town of Mendocino, produced thirteen protein reactions in 499 tests, which was 2·6 per cent. of the total, or 8 per cent. if only negative Schick reactors are considered. In another place in the same report it is noted: '*Diphtheria had recurred epidemically* in Lodi over a period of three years'—on referring to the tables once more, the three entries for districts in Lodi indicate that out of 1468 tests 17 per cent. were pseudo-reactors, but if the 67 per cent. positive reactors are excluded, 34 per cent. of the Schick immunes in Lodi were protein-sensitive. (The italics in the above quotations are mine.) The authors of this most illuminating report were apparently not concerned with the peculiar distribution of these protein reactions. To sum up, in California diphtheria has only recently become prevalent as the high susceptibility of the population demonstrates. In Mendocino county, which is mentioned as one of the most isolated districts, the susceptibility to diphtheria, as indicated by the 80 per cent. of the Schick positive reactors, is the highest of all the districts detailed in the report. Also protein or pseudo-Schick reactors are unusually scarce, because few of the inhabitants have as yet been in recent contact with diphtheria bacilli. In Lodi, which is in closer contact with the outer world, diphtheria has given trouble for three years, and the population, although still highly susceptible (67 per cent.), had had plenty of recent opportunities of coming in contact with diphtheria protein, and 34 per cent. of the immune inhabitants were in a state of diphtherical *allergie*, because they had only recently become immune. The pseudo-reaction, although only considered a nuisance by the anti-diphtheria worker, yet should be of great interest to those engaged in the study of sensitiveness to bacterial proteins, and on this account the pseudo-Schick test has been discussed rather fully.

5. *The Pseudo and Positive or Combined Schick Reaction.*

The combined reaction is the chief, if not the only, serious difficulty in reading Schick tests. The reaction caused by diphtheria toxin, and the allergic reactions which are due to other substances in the test injection may appear together. In these cases the reaction is termed a pseudo *and* positive, or a 'combined', Schick reaction. On the control arm there will only be a plain pseudo-reaction, but on the test arm there will be two reactions superimposed. The combined reaction, 24 to 48 hours after injection, is generally larger and often has a deeper coloured centre than the simple pseudo-reaction which is present on the control arm. In many cases it is impossible to distinguish a combined, or pseudo and positive, Schick reaction from a pseudo *and* negative Schick reaction until a few days after the test, when the protein or pseudo element of the combined reaction has begun to fade, by which time also the toxic element of the reaction becomes more characteristic. By the end of a week in over 70 per cent. of combined reactions the control arm is clear of any very evident marks, while the test arm will show a characteristic desquamating Schick reaction. In a few instances a fairly intense and persistent pseudo may be combined with a weak positive Schick reaction, and in such cases the result is frankly doubtful. Since in most series of tests combined positive and pseudo-reactions only form 3 per cent. of the total test results, and as only a third of these are likely to present any difficulty in interpretation, the error in reading Schick reactions should not be on the average more than 1 per cent. Park (8), whose experience of Schick tests in 1926 was reckoned in hundreds of thousands, says 2 per cent. of all pseudo-reactions (not total tests) are frankly unreadable. In America pseudo results average about 15 per cent. of all Schick reactions therefore, according to Park, only 3 reactions in 1,000 are doubtful, and I am inclined to agree with him. O'Brien (7), in 1922, was more cautious, and stated 1 to 2 per cent. of Schick reactions are doubtful, but the doubtful reactors, whose blood sera O'Brien and his collaborators titrated by Römer's method, all had between 1/100 and 1/20 unit of diphtheria antitoxin per c.c. of blood. Therefore doubtful reactions in most cases indicate a considerable degree of antitoxic immunity, since they invariably have some circulating diphtheria antitoxin, even if it is below the 1/30 unit per c.c., which is ordinarily required to inhibit a Schick reaction. However, it is a wise practice, whenever the Schick test is being employed to pick out susceptibles for active immunization, to include any doubtful reactors in the number to be protected; because, for propaganda purposes, a case of diphtheria arising in a boy who has been told he is immune would be disastrous. It probably needs considerable experience in conjunction with accuracy of technique before the error in reading Schick tests can be reduced below 1 per cent., but very little experience is necessary to reduce the error to 2 per cent., provided a control injection is always used, the tests are checked at the end of the week, and *the toxin is beyond suspicion.* Weak, or faintly positive, Schick reactions and combined Schick reactions are nearly

always an indication that their possessors are shortly about to become Schick immune. It is almost invariably found that in the uninoculated individual such a reaction means that only one dose of prophylactic, or even the Schick test itself, will be sufficient to raise his circulating diphtheria antitoxin above the Schick test level. Zoeller (16) similarly states that all subjects who give a local reaction to 'anatoxin' (a prophylactic antigenic product of the diphtheria bacillus) only require one inoculation to produce immunity; whereas those who do not react require two or more, and since Zoeller also has shown that his 'anatoxin' reaction runs parallel to the Schick combined reaction, it is legitimate to conclude that most pseudo- and positive Schick reactors are already semi-immune, and little harm will result from misreading them as pseudo and negative reactors in routine Schick work. But if the rule of including all doubtful reactions for active immunization is strictly adhered to, there can scarcely be any chance of missing a susceptible individual.

6. *Summary of the Technique and the Reading of the Tests.*

An intradermic injection of 0·2 c.c. of the test solutions is given into the skin of the flexor aspect of each forearm. The left arm is generally used for the test proper, which consists of an injection of a diluted diphtheria toxin, 0·2 c.c. of which contains 1/50 of a M.L.D. The same quantity of the same fluid, which has been heated to destroy the diphtheria toxin, is employed on the right arm as a control.

A. If nothing appears within a week at the site of either control or test injection the subject is a plain Schick negative or immune reactor.

B. If a red patch appears at the site of the test injection, and there is no redness at the site of the control insertion, the test is positive. There is more than 1/40 of a unit of diphtheria antitoxin per c.c. of the subject's blood, and he is a plain positive or susceptible Schick reactor.

C. If a reaction of equal intensity and size appears on both arms, which fades in the course of a week, the subject has a pseudo-Schick, or protein, reaction, but his Schick reaction proper is negative and he is immune.

D. If there is a lesion on both arms, but the one on the test arm is larger, redder, and more persistent than that on the control arm, the individual has a pseudo- or protein reaction 'combined' with a positive Schick reaction.

Illustrations which represent these different types of reaction can be seen in the Medical Research Council's monograph on Diphtheria (17).

(7) *The Reliability of the Schick Test as an Indicator of the Presence of Diphtheria Antitoxin in the Blood.*

Nearly every worker who has had much experience with the Schick test is perfectly satisfied that a negative Schick test, provided that it has been performed with a reliable toxin, is a certain indicator that some diphtheria antitoxin is

present in the blood. This is the opinion of Park and Zingher in America and Glenny and O'Brien in England, who are probably the most experienced workers with the Schick test on the opposite sides of the Atlantic. O'Brien (7) and his collaborators showed that 66 blood titrations by Römer's method were in complete agreement with the statement that less than 1/30 of a unit of antitoxin per c.c. of blood will fail to inhibit a Schick reaction. They also found the blood sera of four subjects in whom the Schick reactions was doubtful all contained over 1/30 of a unit of antitoxin per c.c. But people, unfamiliar with the test, and who bear in mind the vagaries of most skin reactions of the allergic type, find it hard to realize that a positive or negative Schick reaction comes into quite another category of certainty. Since, however, some writers have criticized the Schick tests reliability as an indicator of circulating human diphtheria antitoxin, it may be as well to consider some points which have been raised in opposition to Schick testing.

Kellog (18) has summarized the objections to the Schick reaction as well, and as reasonably, as anybody. It is said that if a Schick test toxin is not carefully standardized and controlled false results will be registered. At first this seems such an obvious remark as to be unworthy of notice, as no one expects to get reliable results if he works with unreliable or bad reagents. But Kellog is quite right to stress this point. It is not generally known, outside laboratories, that a dilute solution of diphtheria toxin will deteriorate rapidly in contact with phenol and other antiseptics, or even simple shaking will destroy it, as Glenny and his collaborators have shown (19). A good example of how an error due to this cause might have never been discovered, and a false inexplicable series of Schick tests put on record, came under the writer's observation. As a visitor to a New Zealand laboratory I was invited to drive 50 miles into the country to inspect some Schick test results. The community was such as would have been expected to show a high percentage of positive reactors, but only about 40 per cent. of the children showed very faint and uncharacteristic reactions. I suggested there was something the matter with the toxin, and elicited the fact that, as it had been diluted in the laboratory before being taken a 50 miles' drive along Colonial roads, it seemed not unlikely that the toxin had been shaken to bits. I heard subsequently that the negative reactors of this series were re-tested with toxin, which was this time diluted at the place of testing, and 62 per cent. of the children, who had been previously recorded as being negative, gave typical positive Schick reactions, raising the percentage immunity of the district from about 40, according to the first investigation, to 80 with the reliable toxin.

Leete (20) also reports how he used a deteriorated toxin and got only 19·5 per cent. of positive reactions among 180 subjects, whereas when he obtained a reliable toxin from O'Brien the percentage of positive tests rose to 57, which was about the usual percentage to be expected in the class of subject he was testing. Thus it is seen the danger of unknowingly using a poor toxin is a very real one. Diphtheria toxin for the Schick test must either be diluted immediately before use and kept out of contact with phenol, or else a properly buffered diluent,

such as described by O'Brien, O'Kell, and Parish (21), must be used. Experience has shown that properly prepared Schick toxin, and outfits for the test, will travel all over the world and keep their full potency for months if this special diluent is used. The stability of the Schick test toxin, when made up with this diluent, has been submitted to a severe test by Joe and McEntee (22), who performed a series of parallel tests on 400 children. These children were tested at the same time with a freshly diluted toxin, and one which had been made up some time previously. All the old solutions, which had been kept for various times up to four months before use, gave the same Schick test results as the freshly diluted toxin. The universal use of such a diluent for Schick testing should in future greatly diminish the chance of getting false immunity readings from deterioration of toxin in dilute solution.

Kellog (18) further states that the error in reading pseudo-Schick reactions may amount to 50 per cent. (of pseudo-reactions), because pseudo-reactions vary so in type and colour, and may be indistinguishable from the specific toxic reaction. This experience seems at variance with that of every other worker. Park for example, as previously mentioned, admitted that 2 per cent. of pseudo-reactions were impossible to read with certainty, but a 50 per cent. error is inconceivable, if a control test is used, and doubtful reactions are checked at the end of the week. Kellog also objects to the Schick reaction because he says the reaction may be negative and positive at the same time on different parts of the same person. Such an interesting result must, however, be extraordinarily rare, as the complete agreement of Joe and McEntee (22) double tests clearly show. I have done many Schick tests in parallel series, re-tested some hundreds of Schick reactors, and never came across any evidence of this phenomenon. O'Brien (21) and his colleagues have also carried out many series of tests in parallel while trying out different Schick toxin diluents, and also have never had cause to suspect this phenomenon. It must be such a rare event as not to be a practical objection, and can probably only occur in a case just on the borderline of the Schick level of toxin (i. e. 1/30 unit per c.c.). Kellog (23) in another paper proposes a modification of the Römer technique as a substitute for the Schick test. In the 'Kellog test' a standard amount of the patient's serum is mixed with a standard amount of toxin and the mixture injected into a guinea-pig's skin. The quantity of toxin is such that 1/30 of a unit of antitoxin per c.c. of serum will just neutralize it; hence, if the guinea-pig gives a positive reaction, the patient that the serum used came from has less than 1/30 of a unit of antitoxin per c.c. of his serum, and should therefore be a positive Schick reactor. Kellog says his test runs exactly parallel with the Schick test in non-immunized individuals, i. e. uninoculated subjects always give the same results, whether tested by Kellog's or Schick's method. Kellog has thus proved the value of his own test by using as a control a test that he has condemned as unreliable, which seems a little inconsistent. In the case of subjects who have been artificially immunized by a diphtheria prophylactic, the Kellog test will sometimes be found positive when the Schick test is negative. This most interesting observation will

be referred to again in section 12. In my opinion I do not think Kellog has made a good case for abandoning the simple Schick procedure for a complicated laboratory test requiring a skilled immunologist. However, in fairness, it is admitted the Kellog test has some advantages, and, in places where a laboratory and immunologist are at the disposal of the anti-diphtheria worker, a routine for collecting mass samples of sera and testing them in batches should not take much more time and trouble than the similar procedure for Wassermann reactions, where a hundred or more tests can easily be done in a day. Opinions on these matters often depend on environment. Kellog works in California, and it has already been pointed out that the protein reactions in certain parts of California were unusually prevalent, and that this excess of pseudo-Schick reactions could not be attributed entirely to the type of Schick toxin used. The 'Sonoma State Home' in California, which Kellog (24) mentions as being the source of some of his material, is included in the report (14) which was previously quoted from. The statistical tables in this report show that of 1688 subjects, 22 per cent. were positive Schick reactors, and no less than 32 per cent. of these gave a pseudo-reaction combined with their positive Schick reaction. Conditions, where one out of every three positive reactors has a protein reaction as well, must be unique in the annals of the Schick test, and one is no longer surprised that Kellog was not enthusiastic over the Schick test. It is of great interest to note that the writers of the report on California Schick tests expressly state they were asked to investigate the Sonoma home because of the *recent* epidemics of diphtheria in it. It would almost seem that the Schick testing had coincided with the moment when a third of the susceptible population had just had time to develop *allergie* towards the protein of the diphtheria bacillus, but had not as yet had enough time to develop circulating antitoxin.

The Schick test is chiefly used to select children for active immunization against diphtheria. Diphtheria prophylactics are perfectly harmless if properly supervised. Park (25) for example states that over 2,000,000 prophylactic inoculations have been given in New York without a single serious accident. Therefore, the opponents to Schick testing argue, it is better to immunize all children, without a preliminary immunity test, in case some real susceptibles escape immunization owing to a false Schick test result. Such a procedure has been a common practice for infants in many places, but I do not think it is a sound practice unless over two-thirds of the population are susceptible. If, as is usual in most samples of a town population, more than 50 per cent. are Schick immune, a preliminary Schick test will save time and economise in prophylactic material. If all reactors about which there is the slightest doubt are included, for immunizing purposes, as susceptible, there need not be the least fear of leaving a non-immune unprotected. In a county like California omitting a preliminary Schick test may be a sound and economical proposition, since most of the groups tested contained over 60 per cent. of susceptible reactors.

8. *The Reliability of the Negative Schick Reaction as an Indicator of Immunity from Clinical Diphtheria.*

In a residential school, during a certain period, when the average population consisted of 180 positive and 800 negative Schick reactors, the Schick reactions of 24 boys, who were notified as clinical diphtheria, were known shortly before the onset of their symptoms. In twenty-three instances the reaction was positive, and in only one boy, who had been notified as diphtheritic, was the reaction negative. These cases were diagnosed by a clinician who, at the time he notified them, was unaware of their Schick reactions. Therefore the incidence of *notified* diphtheria was one hundred times greater in the positive than the negative reactors. It would be hard to get more trustworthy evidence than this of the efficiency of the Schick test in picking out those who are susceptible to diphtheria. In no biological procedure, in combination with clinical diagnosis, can one expect to obtain a 100 per cent. agreement. Park (8) states that in his vast experience he has never seen an *undoubted* case of diphtheria in a subject whose Schick test had been found negative by an *experienced* operator. Of course this statement depends entirely on the definition of 'undoubted case' and 'experienced', but it does imply that typical membranous diphtheria must be very rare in negative Schick reactors. But when patients with sore throats, which do not clinically resemble typical diphtheria, are considered, the matter becomes more difficult. Undoubtedly many cases of simple non-membranous sore throat do occur, from which virulent diphtheria bacilli can be isolated, and in which the Schick reaction is negative. I have gone carefully into this subject, and though the work is not yet published in detail, it is summarized elsewhere (26). Suffice it to say here, such cases are probably in most instances merely coincident infections in carriers and not true diphtheria patients, i.e. the throat lesion is not caused by toxins of *C. diphtheriae*, but is due to a coincident infection with some other organism. While it is readily admitted that some of these patients may be mild cases of diphtheria in partially immune subjects, yet any cases which are diagnosed as diphtheria in definite Schick negative reactors are never severe. As Harries (27) has pointed out, even if a pseudo-membrane is seen in such a case, it strips easily without leaving a bleeding surface, and the patient is never bad enough to make anti-toxin treatment essential. Schick negative reactors who are suffering from sore throats, which do not resemble typical membranous diphtheria clinically, but yet contain virulent diphtheria bacilli, are thus of little practical importance therapeutically, and it may seem to be of merely academic interest whether they are considered to be diphtheria carriers who are suffering from a coincident tonsillitis which is not caused by diphtheria toxin, or mild cases of specific diphtheria. The point is, however, of considerable importance in other respects. Undoubtedly at certain times, and in certain environments, such as large residential institutions, the carrier rate for *C. diphtheriae* becomes very high, and at the same time simple 'sore throat' is often very common. In such environments many individuals may be found with the combination of simple sore throat,

negative Schick reaction, and 'positive K.L.B.' Of course, if the organism termed 'K.L.B.' is subsequently proved to be non-toxigenic, such a case need not be diagnosed as diphtheria; but a medical practitioner who has received the common laboratory report 'K.L.B. present' with regard to a case which, while not typically diphtheria, may become so, has to notify and treat his patient as diphtheria, unless he happens to know if the strain of 'K.L.B.' is virulent or not, and the result of the patient's Schick reaction: information rarely available in ordinary practice. If the organism is toxigenic, but the Schick test negative, it will depend entirely on the clinical and bacteriological prejudices and the psychological qualities of the medical attendant as to whether or not the case is diagnosed as diphtheria. Such atypical sore throats account for the majority of reports condemning the Schick test as a poor indicator of immunity, which is my chief reason for dwelling on this subject.

The following are references to some of the cases of diphtheria which are reported in the literature to have occurred in negative Schick reactors:

Joe (28) states that thirteen cases of diphtheria in Schick negative reactors were notified in Edinburgh. In Joe's opinion, four were not diphtheria at all, six were carriers, and three mild cases with atypical sore throats. This is a good illustration of how notification returns may become unintentionally falsified. Massingham (29) reported three 'mild cases' of clinical diphtheria in hospital nurses, whose Schick reactions had been recorded as negative, but who had been nursing a tracheotomy case. The blood of one of these nurses was titrated by Römer's method at the time she got diphtheria, and was found to contain only 0·005 of a unit of diphtheria antitoxin per c.c., therefore, by rights, she should have given a positive Schick reaction. Haidvogl (30) describes nine nasal and three faucal cases of diphtheria which had Schick negative reactions at the time of their illness and whose blood sera contained from 0·04 to 0·5 of a unit of antitoxin per c.c. The exact time these patients had their blood examined is not quite clear, but it was after the onset of symptoms. It is therefore conceivable, if not highly probable, that their Schick reactions were positive at the time of their infection; and therefore the anti-toxin in the blood, which was responsible for the negative Schick tests, had been stimulated as a result of their illness. Peters (31) expressed the opinion that nurses who had negative Schick reactions were almost as likely to contract diphtheria as nurses with positive reactions, but he gave no details as regards the type of infection, or the relation of the Schick immunity, to the onset of illness. In a subsequent communication Peters (32) admitted that none of his hospital nurses, who had received three inoculations of toxin-antitoxin mixture, had contracted diphtheria. Unfortunately this author must have had some misfortune with his Schick toxin, because he reports that two different samples of toxin were tested out on the same eleven subjects. One toxin produced three, the other six, negative reactions. Peters considered this was 'a truly alarming discrepancy', and I cordially agree with him. Peters' experience with the Schick test and fever hospital nurses is completely at variance with Joe's (28) in Edinburgh, Kinloch Smith and Taylor's (33)

in Aberdeen, and Harries', as reported by Forbes (34), in Birmingham, all of whom speak favourably on the reliability of a negative Schick reaction as an index of the immunity of hospital nurses from clinical diphtheria.

An unbiased sifting of the total evidence leads to the conclusion that, in a case which at the time of onset of symptoms is definitely diphtheria from the clinical point of view, the Schick reaction is invariably positive; but atypical and modified cases of diphtheria do occur at times in Schick negative reactors, especially when the subject has been submitted to the risk of massive doses of infection, as was the case with Massingham's nurses. As Peters (32) wisely remarks, 'it is well to consider, like everything else in medicine, that these methods (i.e. Schick testing and active immunization) are not absolutely infallible'.

Although I have hunted the literature for well-substantiated cases of diphtheria in negative Schick reactions the above examples are as good as any found. Before it can be said that typical membranous diphtheria can originate in an individual who has a negative Schick reaction it is essential that there is no doubt: First, of the clinical diagnosis. Secondly, that a real toxigenic strain of *Corynebacterium diphtheriae* has been isolated from the throat. Thirdly, that the Schick test was negative before the onset of symptoms, and the toxin used for the test was above all suspicion. The onus of producing a reasonable number of cases which satisfy these three criteria rests with those who criticize the reliability of the negative Schick test as an indication of immunity to clinically diagnosable diphtheria, and so far no one has done so.

9. *The Schick Test: Subsequent Prophylactic Inoculations against Diphtheria.*

The importance of demonstrating that a Schick negative reaction is incompatible with *severe* diphtheria cannot be overstated. In the last section it was concluded that this proposition was probably true in the case of the natural Schick negative reactor; but it is of equal importance to decide if the Schick negative reaction which is produced by the mechanical inoculation of a diphtherial antigen is also a reliable criterion of immunity to severe diphtheria; because on this point depends the whole rationale of modern diphtheria prophylaxis. There have been a fair number of reports which state that severe diphtheria has originated in 'immunized' individuals. Examination of these statements, when sufficient data is given, invariably shows that the case of diphtheria in question did not originate in an 'immunized' subject but in some individual who had received one or more injections of a diphtheria prophylactic, and in whom, either no subsequent Schick test had been performed, or, if it had, the test was positive, which of course indicated that the attempt at immunization had failed. The application of the term 'immunized' to some one, in whom an attempt has been made to artificially stimulate the formation of specific antibody, is to be deprecated, unless it is known the attempt was successful. Any one, who has tried to immunizeactively a group of children against diphtheria, knows that there will always be 5 to 10 per cent. of the group who will not become Schick negative

with the routine course of prophylactic inoculations. It is these bad anti-toxin formers to whom it is especially important to give more and more doses of prophylactic until they do ultimately become Schick immune; because it is undoubtedly among this group that the worst cases of diphtheria are prone to arise. Friedmann (35) has even gone so far as to suggest that it is only this group of subject who resist the attempts to immunize them who suffer from clinical diphtheria; and that ordinarily those Schick positive reactors who become immune with the routine course of two or three doses of a diphtheria antigen would, in any case, become either latently immunized bacillary carriers or subclinical, rather than typical, diphtheria cases, when they come in contact with diphtheria infection. To support this somewhat discouraging theory Friedmann (35) relies on the well-established fact that about 50 per cent. of diphtheria convalescents are found to be positive Schick reactors, and argues that if an attack of clinical diphtheria itself is not sufficient to stimulate the production of circulatory antitoxin it is unlikely that the injection of laboratory-made prophylactic can do so. The fact is true enough, but the theory based on it is probably false because, under suitable conditions of the environment, the positive reactions in diphtheria convalescents will, in the aggregate, become negative more rapidly, and with less intense stimulation, than the positive reactions of subjects who have no past history of diphtheria (see sect. 14). Probably most convalescents from diphtheria were bad antitoxin producers before contracting their illness, which was partly the reason they became ill, and it is therefore highly desirable to produce Schick immunity in those subjects in which it is most difficult to do so. For this reason a Schick test, subsequent to a prophylactic course, must never be omitted in order to discover if the attempt to stimulate circulatory diphtheria antitoxin has succeeded.

In order to save the extra time and inconvenience to both medical man and patient that repeated Schick tests and prophylactic inoculations involve, several attempts have been made to devise a preparation which will act as a prophylactic and, at the same time, indicate the immunity reaction of the inoculated subject. Glenny and Waddington (36) have been experimenting in this direction, but, at present, the technical difficulties in balancing a dose of Schick toxin with one of the modern diphtheria prophylactics, and the great experience which is needed to interpret the immunity reaction in the presence of the marked increase of pseudo-reactions which are produced by the combined immunizing and diagnostic preparations, makes their general use inadvisable. Park (37), according to some comparative figures of Schick and 'Park' tests in a U.S.A. report, apparently produced a fairly satisfactory toxin-antitoxin mixture which also acted as an indicator of the subject's immunity; but since, nowadays, preparations containing unmodified toxin have been practically discarded in favour of non-poisonous prophylactics, the so-called Park test has little practical value, because it would be a very retrograde step to return to the use of prophylactics which contained unmodified diphtheria toxin. Perseverance along these lines of research is to be encouraged, because the alternate Schick tests and prophylactic inoculations,

which may have to be repeated many times on those refractory individuals in whom it is especially important to produce immunity, tend to exhaust the patience of both doctor and subject. In such cases a combined diagnostic and immunizing preparation would about halve the number of injections and examinations at present necessary, and this would be an inestimable boon to the anti-diphtheria worker.

10. *The Persistence of the Schick Negative Reaction.*

For administrative purposes in the field of preventive medicine it is most essential to know how long the immunity produced by active immunization may be expected to last. In other words, how long does a Schick negative reaction persist? Are relapses to a positive from a negative reaction frequent, and if so, when do they occur? Most of the evidence suggests that the Schick negative reaction is, in the majority of cases, permanent, as may be inferred from the fact that the majority of town-bred adults are Schick negative reactors, and that the percentage of negative reactions, in nearly all populations, steadily increases with age. But this deduction applies only to the naturally acquired negative reaction. As regards the artificially induced negative Schick reaction, Park (8) stated in a recent paper that over 90 per cent. of those children who had been successfully immunized were found to retain their negative reactions when re-tested nine years later. Parish and O'Kell (38) have investigated this question in England; 440 children, originally Schick susceptible, who had been successfully immunized, were re-tested at periods of one to seven years, and 22 were read as Schick positive at the re-test. Therefore 95 per cent. had remained Schick immune. These figures are eminently satisfactory, especially when it is found that the twenty-two relapses, with only one exception, responded at once to a single fresh dose of diphtheria prophylactic, or even to the Schick dose of toxin itself. Therefore, although the reaction had relapsed, these subjects were in a sensitive state and responded rapidly to a fresh antigenic stimulus. If not exactly Schick immune, they were basally immune, as will be discussed in the succeeding section. Gorter and Huinink (39) reported nine artificially induced Schick negative reactions relapsed to positive after an interval of eighteen months to two years. All these cases, however, retained an appreciable amount of diphtheria antitoxin in their blood, but it was below the Schick level (1/30 unit per c.c.), and all responded at once to a single dose of toxin-antitoxin mixture more rapidly than they had done at their first immunization. These observations apply to those Schick negative reactions which are produced by artificial means. In the case of the natural Schick negative reaction the tendency to relapse to positive seems even less than in that produced by a diphtheria prophylactic. Parish and O'Kell (38) also re-examined 533 natural Schick immunes, and at the re-tests, one to seven years later, only found six (1·1 per cent.) to have a reaction which was read as positive. I re-tested 308 boys, originally natural negative Schick reactors, at intervals of nine months to two years and only discovered one which was read

as positive at a re-test. But even this one relapse, to my mind, is so surprising, considering the environment the subject had lived in, that I am rather inclined to attribute this isolated exception to a technical, or clerical, error in the records than to a real loss of immunity. The antigenic stimulus of the environment in Greenwich Hospital School was so high that it is almost inconceivable that the antitoxin content of the blood of any boy who had once become immune, and had remained in the school, could fall again below the Schick level. There are, however, some reports which infer that the Schick negative reaction may not be as stable as the above experience leads one to believe. Therefore it is advisable to examine one or two reports wherein Schick negative reactions are alleged to have relapsed frequently.

In 1922 an editorial published in the United States Naval Bulletin (40) states that 'most (American) naval medical officers have reached the conclusion that immunity as recorded by the Schick test is not constant. *Large numbers* of men who had given negative Schick tests on one occasion were tested several months later and a *considerable percentage* were found to be positive, i. e. susceptible to diphtheria. This could not be explained entirely by the personal factor because the same medical officer made all the readings on both occasions. These observations were made by Hughens at Great Lakes and Houghton at Annapolis. At Annapolis, in the fall of 1918, all susceptible individuals were immunized . . . the *entire personnel* was Schicked again, and of 1,147 who had received toxin antitoxin 22 per cent. gave positive tests'. (The italics are mine, S. F. D.) Overlooking the vagueness of 'large numbers' and 'a considerable percentage', and the fact that Schick susceptible and diphtheria susceptible are not interchangeable terms, it seems that relatively many more American sailors relapsed than was the case with the material Parish and O'Kell re-tested. If the expression 'entire personnel' is meant literally in the above quotation, it would mean that at least 1,000 originally natural negative reactors had been re-tested at Annapolis. The context in the quotation also seems to imply that the '22 per cent. positive reactions' had previously been negative. However, such a meaning is probably not intended, because a search through the files of the United States Naval bulletin reveals that Houghton (41) in the autumn of 1918 had tested about 2,600 men, chiefly American midshipmen, and had found about 50 per cent. were Schick susceptible. These Schick positive reactors, who must represent the 1,147 in the above quotation, were all given three doses of a toxin-antitoxin mixture. There is no mention that any Schick tests were performed subsequent to the prophylactic injections. It seems therefore that the '22 per cent.' were only those bad antitoxin formers which the three doses of prophylactic in the routine course had failed to immunize. As a matter of fact, to get 78 per cent. out of the Schick positive reactions of a population, only half the members of which were Schick immune to start with, to become negative in six months with only one course of prophylactic inoculations is just about what was to be expected. The whole report is only an interesting lesson that 'immunized' and 'inoculated' are not synonyms. I could find no further detailed

evidence in the U. S. Naval Bulletin between 1918–1924 that a single negative reaction had relapsed, much less that 'a considerable percentage' of previously negative Schick reactions had become positive on re-testing.

The result of an inquiry instituted by Schwalbe (42) shows that the Schick test and active immunization for diphtheria prevention is, in general, not raising much enthusiasm in Germany. According to Schwalbe, Professor Birk of the Tubingen Children's clinic in Wurttemberg is highly critical: he states 'during the Schick tests given a few months after immunization (*sic*), no marked changes in the ratio of negative and positive occurred. A few children positive became negative, but others who had been negative became positive . . . immunization was not successful till after a year had passed, when positive reactions had been reduced by half . . . in some children the test fluctuated . . . there was no assurance that a child once negative would remain so'. According to Birk's Schick statistics, reproduced in Schwalbe's report (42), his children between the ages of one and ten years of age were about 60 per cent. naturally immune. Therefore if he had used an efficient prophylactic, and if his Schick toxin had been reliable, he should have certainly got more than 50 per cent. of his susceptible subjects immune within a year (see section 22). I do not know the recent incidence of diphtheria in Tubingen, but either it was markedly prevalent to account for the high original immunity of the young children, or Birk had some misfortune with his Schick toxin, such as the accident in New Zealand, previously mentioned (see section 7). Schwalbe states that during recent years the distribution of diphtheria in Germany has been most irregular, being almost absent from some districts while epidemic in other places, such as Berlin. It is not improbable that Tubingen had been relatively free from diphtheria for some years, because, according to Birk, there was no significant difference between the Schick immunity of five age groups of children ranging from three months to ten years of age (see Fig. 3, section 23). The absence of any age gradient in *combination with the slow rate of immunization* are indications of a highly susceptible unsalted community. If this was so, the high herd immunity, which 60 per cent. of negative reactors would indicate, is only apparent, and must have been caused by the use of a weaker test toxin than is usual elsewhere. It is conceivable that these three factors, insufficient prophylactic, unreliable Schick toxin, and lack of natural antigenic stimuli in the environment, would account for a number of children acquiring an amount of circulatory antitoxin which was about equivalent to the average 'Schick level'; if so, very slight variations, in the dose of the Schick toxin, or the quantity of antitoxin in the blood of the tested subject, might possibly account for the alternating Schick reactions which Birk complains of. His experience only seems to be another example of insufficient prophylactic injections, in conjunction with a weak Schick toxin, otherwise it is entirely inexplicable, unless all other English, French, and American observations on Schick immunity are at fault. There is, however, one series of English Schick tests by Harries which at first sight seem to show percentage differences in Schick immunity which are inexplicable, unless a large number of

natural Schick negatives in the population had relapsed between the beginning and end of 1927. Harries (27) gives a table of Schick tests of what seemed to be comparable, random, and sufficiently large samples from the same social class of Birmingham children. The percentage of Schick immunes in the sample which was tested in the first quarter of the year was 60 ; while in the third quarter of the year a different sample of the same class was only 30 per cent. immune. There were no actual re-tests. It is impossible to suggest, with a fever authority like Harries working in conjunction with O'Brien, such a discrepancy as 30 per cent. was due to technical errors or personal equation. The numbers of those tested were too large for chance in sampling to explain away the whole of the 30 per cent. difference. Besides two other samples, tested in the second and last quarter of 1927, and the details for different age groups in the tables, all confirm the conclusion than in 1927 in Birmingham, in spite of the prevalence of diphtheria, many of the children must have lost their Schick immunity. I was very loath to accept this conclusion, which was at complete variance with my concepts of Schick immunity in relation to the environment ; but it was some time before I realized Harries' figures have a rational explanation which does not necessitate that a single negative reaction should have become positive. To discuss adequately how this was possible would take too long, and is not relevant to my subject ; but, in case any one else is worried over Table IX in Harries' (27) invaluable contribution to the elucidation of latent immunization in scarlet fever and diphtheria, I will just roughly indicate the nature of the mechanism by which the seasonal fluctuation in the Schick immunity of Harries' different groups could have taken place. The false conclusion was arrived at, on the false assumption that the samples were a *random* selection of the Birmingham population with regard to their Schick immunity. These seasonal Schick tests were performed on some 700 *consecutive cases of scarlet fever.* Scarlet fever selects individuals with positive Dick tests. Dick positive reactions are found in Schick positive reactors much more frequently than in the population as a whole ; therefore scarlet fever will tend to select positive Schick reactions. Attacks of scarlet fever, diphtheria, and latent immunity to these diseases, are acquired in a similar way, but not exactly at the same rates and times. With a suitable differential rate of immunization and seasonal incidence for the two diseases, it is possible for scarlet fever to attack a higher proportion of Schick positive reactors during one season of the year than another.

However, the question of a fluctuating Schick immunity must not be dismissed too lightly. The observations which support the stability of the negative Schick reaction have practically all been made on town-bred children, who live in environments where the opportunities of frequent subinfections with diphtheria bacilli are great. For this reason further observations on the stability of the Schick immunity are badly wanted from isolated, or rural, districts which have not been afflicted with diphtheria for some years. It is possible that in the absence of more or less frequent antigenic stimuli from the diphtheria bacilli in the environment, the antitoxic titre of a blood which had been once above

Schick level might drop below it more often than is suggested by the observations made in towns. With regard to this speculation it is of interest to note that Glenny (43) has published charts of the natural diphtheria antitoxin titre in the blood of two normal uninoculated horses. One curve shows fluctuations in the antitoxin titre ranging from 0·01 to 1·25 units per c.c., the other from 0·0005 to 0·04 of a unit of diphtheria antitoxin per c.c. of blood. These fluctuations in the antitoxin content took place within two or three months. Such oscillations in a human subject would have placed him below and above the Schick level of 0·03 unit per c.c., and he would have given alternating positive and negative Schick reactions if tested at the appropriate moments. Finally some one has suggested that the antitoxin content of the blood may be decreased by infections other than diphtheria. If so, an attack of measles, or any other infection, might change a negative Schick reaction to positive. Leete (20) thought his Schick statistics indicated that scarlet fever increased the susceptibility to diphtheria, but the discussion of Harries' work, given above, shows how such an idea could arise. There is no evidence that other infectious diseases can cause any diminution of an individual's Schick immunity; but since the degree of immunity to diphtheria, scarlet fever, and probably many other infections, is a function of the degree of previous exposure to the specific causative agents, it follows that exposure to several kinds of infection may tend to occur to a similar extent in the same individual according to his environment. Therefore, as was demonstrated by Harries to be the case for scarlet fever, other infections such as measles or whooping cough may be able to select a group of children who contain more susceptible Schick reactors than the average, and in this way convey a false impression that the infection itself could diminish the titre of diphtheria antitoxin in the blood.

11. *Primary and Secondary Antigenic Stimuli.*

In order to appreciate the Schick reaction in its relation to immunity to diphtheria, it is absolutely essential to thoroughly grasp the concept of primary and secondary stimuli.

Glenny and Sudmersen (1921), (44), and Glenny and Allen (1922), (45), published work which showed that when a dose of diphtheria toxin-antitoxin mixture is given to an animal, which has never been inoculated before, and which has no diphtheria antitoxin in its blood, there is a latent period of about three weeks before any antitoxin can be detected in the animal's blood. Antitoxin then appears, and its quantity gradually increases to reach a maximum about eight weeks after inoculation. The antitoxin titre then slowly declines. This is the type of response to a primary antigenic stimulus in an animal with no previous experience of the antigen employed. If, after all, or nearly all, the antitoxin has disappeared from the blood of an animal which has had such a primary stimulus, a second injection of toxin-antitoxin mixture is given, antitoxin reappears in three days instead of three weeks, and the antitoxin titre

reaches its maximum in about eight days instead of weeks. Moreover, the quantity of antitoxin produced is 10 to 100 times the amount produced by the original primary stimulus. An antigenic inoculation which produces this type of response is termed a secondary stimulus. Thus, in an organism that has been sensitized by an antigen, although no antibody may be present in the blood, yet the animal, as regards its immunity, is in quite a different state to one which is not so sensitized. Such a sensitized, or experienced, animal may respond to further antigenic inoculations, or secondary stimuli, even if of very much smaller intensity than the primary stimulus, by making antibody at ten times the rate and ten times as potent as an inexperienced animal. Glenny and his collaborators have demonstrated that these two types of response to primary and secondary stimuli are probably of general occurrence, and take place with many of the specific antigen-antibody reactions in the animal organism. The conception of primary and secondary stimuli is of fundamental importance in understanding the phenomena of immunity to infectious disease. It is also of great practical importance in vaccine therapy, as Glenny's researches have explained the necessity of correctly spacing curative and prophylactic injections, if the best results are to be obtained. Glenny (43) has recently summarized his own, and other workers' views, on the principles of immunity as applied to diphtheria, in a masterly paper, which no one interested in the subject can afford to miss reading. The primary and secondary stimuli concept explains the fact that nearly all observers of any experience (such as Parish and O'Kell (38)), report that the few relapses, from Schick negative to positive, which have occurred after active immunization against diphtheria have, with very few exceptions, responded immediately to a single dose of a diphtheria antigen, even though the original immunity had taken much time and trouble to produce. The first course of prophylactic injections had acted as a primary stimulus enabling a much less intense second course to act as a secondary stimulus. O'Brien (46) has shown that even the minute dose of diphtheria toxin contained in the Schick injection is often sufficient to induce a rise in the antitoxin titre of the blood from below to above Schick level (0·03 units per c.c.). One of O'Brien's cases, a child who had been actively immunized and made a Schick negative reactor, was later found to have again become a positive reactor. Her blood the day after the test contained less than 0·004 unit per c.c. of diphtheria antitoxin. A week later her Schick reaction was negative, and the blood contained between 0·1 and 0·5 of a unit per c.c. Hence the very Schick test, by which it is discovered that a subject has lost his immunity, is often a sufficient stimulant to restore it. As O'Brien remarks, 'the magnitude and rapidity of the "secondary response" will convince any one that the so-called "negative phase" is of no importance in active immunization of human beings'. It had been stated, by some of the critics of active immunization in diphtheria, that the prophylactic inoculations make the recipient temporarily more prone to an attack of diphtheria owing to the 'negative phase' which they alleged followed the injection. To my mind these observations have a far greater importance than merely removing the fear of

a mythical negative phase, because they show that even if the aphorism 'once Schick negative always Schick negative' is not literally true, that for the practical purposes of diphtheria prevention the statement is true. Almost every one, in whom a Schick negative reaction has once been provoked, remains so sensitive to further secondary stimuli from diphtheria antigens, that even should he loose his negative reaction, it does not matter much; because, if a dose of diphtheria bacilli is subsequently encountered, the antitoxin response is of the type produced by a secondary stimulus, and is so rapid and strong that the infection has no time to produce any but the most trivial symptoms. Harries (27) describes some clinical observations which also support this hypothesis.

12. *The Immunity of Positive Schick Reactors.*

The preceding section indicates that because an individual's Schick reaction is positive, it by no means necessarily means he is susceptible to clinical diphtheria. The positive Schick reaction only implies that there is less than about 1/30 of a unit of diphtheria antitoxin per c.c. of blood-serum. Titration of the sera by Römer's method shows that in many Schick positive reactors an appreciable quantity of antitoxin is present. Such individuals, and even those where no antitoxin can be detected, may have a high degree of basal immunity. In the paper previously mentioned, Glenny (43) has classified Schick reactors into: the immune Schick negative reactors, who have over 1/30 of a unit of antitoxin per c.c. of blood; then four groups of positive Schick reactors: (*a*) With circulatory antitoxin below 1/30 of a unit per c.c.; (*b*) With no antitoxin, but who respond rapidly to a minute antigenic stimulus, such as another Schick test; (*c*) Those who respond fairly easily to immunizing inoculations; (*d*) The group of slow antitoxin formers who take a long time, and require many injections of prophylactic, before they will become Schick immune. The last group (*d*) are the real non-immunes with no previous experience of diphtheria, and who require both primary and secondary antigenic stimuli before developing circulatory diphtheria antitoxin. Groups *a*, *b*, and *c* are in a descending order of responsiveness to diphtheria toxin, and immunizing injections act on them as secondary stimuli. Glenny calls (*a*) Schick positive immunes, (*b*) potential immunes, and (*c*) sub-immunes. Of course there is no discontinuity between these groups, who all shade gradually into each other. The existence of different degrees of Schick susceptibility is confirmed indirectly by the differential incidence of clinical diphtheria among the inhabitants of an institution. Among the boys of Greenwich Hospital School 223 cases were notified as diphtheria from 1922 to 1927 inclusive. 45 per cent. of these cases arose among boys who had been less than six months at school, 34 per cent. in boys of 6–18 months' seniority, and 21 per cent. among those boys who had been more than 18 months in residence. These subdivisions in the seniority of the population were selected, because each contained on the average about the same number of susceptible reactors during the four-year period. The incidence of diphtheria for the whole of each group, including Schick negative immunes, would

have been: under 6 months' seniority, 16 per cent.; 6–18 months, 6 per cent.; and over 18 months, about 3 per cent. per annum. Whereas the incidence among the Schick positive reactors in each group, when the Schick negative reactors were excluded, was respectively about 36, 25, and 16 per cent. per annum. The incidence of diphtheria was not therefore directly proportional to the relative number of Schick positive reactors in a group, but decreased with the seniority of the group. The average Schick positive reactor in the most senior group was less than half as liable to contract diphtheria as a Schick positive reactor who had been less than six months at school, because the senior groups contained relatively more Schick positive members, who were, what Glenny has termed Schick positive immunes, and potential immunes. In section 22, on 'the rate of active immunization', there is further evidence in confirmation of the hypothesis that all Schick positive reactors, even including those individuals who have no demonstrable circulatory antitoxin, are not equally susceptible to diphtheria. Schick (47) himself in 1921 recognized that the Schick positive reactor was not necessarily susceptible, he says: 'In addition to the local protection derived from an intact mucus membrane there are two factors producing immunity against diphtheria, the one humoral in nature . . . (i. e. circulatory antitoxin), the other is the cellular factor, which is based on the varying faculty of the cells to generate antitoxin'. Schick (1921), however, does not consider 'cellular immunity' of itself able to prevent infection, but that it determines the duration and intensity of attack. It is not certain from the context whether Schick admits that carrier infection without symptoms can originate in an individual who has a Schick positive reaction. But I think certain observations, made since 1921, strongly suggest that carrier infection can originate while a subject is Schick positive.

Kellog's (24) unique observations that a subject who had been made Schick negative by artificial means might *repeatedly* give positive Kellog tests indicating that he had less than 1/30 of a unit of circulating diphtheria antitoxin, though he continued to give negative Schick reactions, may perchance be explained on the cellular immunity theory. That is to say, certain exceptional individuals have a cellular immunity of their skin which inhibits the Schick reaction, in spite of the fact that there is not enough antitoxin in their blood-serum to neutralize the dose of toxin in Kellog's guinea-pig test. Such a theory is rendered more plausible by some German work (I cannot trace the reference) which indicated that the expressed juice of certain tissues might contain a higher titre of diphtheria antitoxin than the blood-serum. Such subjects, though of great theoretical interest, would almost certainly be immune to clinical diphtheria.

13. *Immunity to Diphtheria other than that due to Antitoxin.*

There are undoubtedly other mechanisms, besides the production of antitoxin, by which the human organism repels the invasion of *Corynebacterium diphtheriae*, and such mechanisms may also explain why some individuals without a trace of circulating diphtheria antitoxin remain apparently immune in spite of exposure

to diphtheria infection. The 'virulence' of the diphtheria bacillus itself does not seem to depend entirely on toxigenicity. The writer (48) for example was able to destroy guinea-pigs, which had been protected with diphtheria antitoxin, with massive intraperitoneal doses of toxigenic *C. diphtheriae*, and also get equally lethal effects with the non-toxigenic variety of the organism. On the human side, Solis-Cohen (49) showed that the blood of certain individuals had a bactericidal effect on diphtheria bacilli, while the blood of others permitted their free growth. Moreover, this property was entirely uncorrelated with the presence or absence of antitoxin in the blood. A Schick positive reactor might have a powerful bactericidal serum, whereas the serum of a Schick negative reactor might have no inhibitory effect on the growth of diphtheria bacilli. Also the pseudo-Schick reaction is an immunological phenomenon which, though distinct from antitoxic immunity, is undoubtedly to some extent correlated with it, as is shown by Zoeller's (13, 16) observations already referred to (section 4), and by the fact that, pseudo and positive reactions become Schick immune more quickly and easily in response to both natural and artificial antigenic stimuli. Finally there is the direct action of the mucus membrane of the nose and mouth, which has been brought out by many experiments, such as those of Bloomfield (50, 51) who demonstrated that *B. coli*, haemolytic streptococci, and other bacteria cannot be recovered from the nose, throat, or tongue, twenty-four hours after their application in massive doses to these organs. The more recent experiments of Arnold, Ostrom, and Singer (52) showed that 90 per cent. of a dose of *B. coli* which had been introduced into the nose disappeared within fifteen minutes. The organisms were not merely washed into the pharynx and swallowed, because cultures which were made from the throat remained sterile in all but one or two experiments. Again, according to these authors, the destruction was a direct action of the mucosa, and not due to a bactericidal effect of the nasal secretion, since nasal washings had no inhibitory effect on the growth of the test organisms. However, Flemming (1921) (53), discovered an agent in the tears, nasal secretions, and other body fluids which has the property of causing bacterial lysis. This agent which was named 'lysozyme' acts most strongly on non-pathogenic bacteria. Ridley (54), who has recently summarized and extended the work on lysozyme, makes the important point, that if the concentration of the agent is too low there may be no sensible effect on the growth of a bacterium, whereas a small increase in the titre of the agent may produce complete inhibition of growth. Provided the concentration of lysozyme is adequate, most pathogenic bacteria are affected. Although heretofore it has been said that diphtheria bacilli are completely refractory to lysozyme yet, in view of Ridley's observations, some such inhibitory action of the naso-pharyngeal secretion on diphtheria bacilli merits further investigation. Digby (55, 56) has also collected a mass of evidence which suggests that the tonsils and sub-epithelial lymphoid tissue is an important organ, part of whose function is the collection and destruction of bacteria, and the manufacture of bacterial antibodies. Such immunity may be independent of circulating antitoxin and remain localized to the naso-pharyngeal mucosa in

a manner similar to the local immunity which Besredka (57) claims for the skin to anthrax, and for the intestinal mucosa to enteric infections. The hypothesis that there is a local immunity to diphtheria is further strengthened by reports of nasal and faucial carriers of diphtheria bacilli who have positive Schick reactions. Although such individuals may be rare, yet I think their existence must be accepted.

14. *The Schick Reaction and Clinical Diphtheria.*

In a preceding section it was concluded that a 'text-book' case of diphtheria invariably had a positive Schick test at the time of the onset of the symptoms. For this reason a Schick reaction is a useful confirmatory diagnostic test, as the clinical signs have to be very definite in order to diagnose diphtheria in the presence of a negative Schick reaction obtained prior to the administration of therapeutic diphtheria antitoxin, which of course inhibits a positive Schick reaction. For practical purposes the diagnosis of an atypical sore throat, which contains virulent diphtheria bacilli, will solely depend on whether the Schick reaction is positive or negative.

In most cases of diphtheria the Schick reaction is found to be still positive after the therapeutic antitoxin has been eliminated. Various authors have reported that 50 or more per cent. of diphtheria convalescents have positive Schick reactions and only a trace of, or no, natural antitoxin in their blood. Park and Zingher (58) (1916), for example, state that 19 out of 32 diphtheria cases had positive Schick reactions 3–4 months, and 12 out of 15 a year, after an attack of diphtheria, i.e. 66 per cent. of the Schick tests, in these subjects who had had diphtheria, were positive. It seems, however, that antitoxin does generally appear after a clinical attack but in too small an amount to inhibit the Schick test; also even this amount disappears again in the course of a few weeks or months. An attack of clinical diphtheria does not therefore seem to be a very efficient antigenic stimulus. Now, if these observations are examined in the light of Glenny's researches on primary and secondary stimuli (vide Section 11) certain points become clearer. It does not seem straining the evidence to suppose that severe diphtheria commonly only occurs in the almost completely unsensitized Schick positive reactor. The patient only forms enough antitoxin to get well, and the average duration of infection is not long enough to stimulate a permanent supply, since the little antitoxin which is found after an attack soon disappears under ordinary circumstances. The attack, however, has acted as a primary stimulus, so that should the recovered diphtheria patient again run the risk of infection, that is, again come in contact with diphtheria bacilli, he receives a secondary stimulus, and, just as in the case of Glenny's experimental animals, responds by a rapid increase of the antitoxic titre of his blood, rather than by a second attack of clinical diphtheria. Two sets of observations which were made at Greenwich strongly support this view. Out of 50 diphtheria convalescents who returned to the school while diphtheria was still prevalent, and who were Schick tested

three to six months after their return, only 8 had positive reactions, the rest were Schick immune. More recently, in 1928, 79 boys who had had diphtheria six months to three years previously were found to include 14 positive reactors, therefore 22 per cent. were immune, which was about the same as that for the rest of the school (excluding first-term boys) who had not had diphtheria and who were 24 per cent. positive. Thus, diphtheria generally attacks the completely inexperienced and immune reactor, who, although he does not often develop Schick immunity as a consequence of the clinical attack, yet has been sensitized so that any further antigenic stimulus results in the production of a negative Schick reaction rather than clinical diphtheria. The other hypothesis is the hereditary one, which postulates that certain subjects are born with poor powers of forming antitoxin, and that these are the persons who get diphtheria, the rest become Schick immune, or carriers, when brought into contact with diphtheria bacilli. Friedmann (35) and others who support this hypothesis, point to the Schick positive reactions of the convalescent diphtheria cases and mention cases who have had second and third attacks of diphtheria. I can, however, find no statistics of the frequency of multiple attacks of diphtheria, which can justify such an opinion. If this hypothesis were true, second, third, and multiple attacks of diphtheria should be very common; as a matter of fact, second attacks of diphtheria, if not rare, are quite uncommon enough to be a subject for remark. In Greenwich School between 1919 and 1927 there were notified 408 cases of diphtheria, 391 of which I have been able to trace in the school and sick records, only 5 of these 391 were second attacks, that is to say, only 5 out of 386 boys or 1·3 per cent. got notified for a second time as clinical diphtheria. As previously mentioned over half the boys were attacked during the first six months of school life, hence it is safe to say that, on the average, boys who had had diphtheria returned to school immune for another two years. The attack rate for the school was 8·6 per cent. per two years. Therefore, even if these recovered diphtheria cases were not more, but just as, prone to attack as the rest of the school including all the natural immunes, at least 33 boys would have been expected to get multiple attacks of diphtheria in lieu of the five who actually did. If the Schick negative reactors are excluded, and susceptible reactors only considered, the expected number of second attacks of diphtheria should be about 132, assuming a recovered diphtheria patient is as susceptible to reinfection as the average Schick positive reactor. According to these figures, an average member of the group of boys in the school who had had clinical diphtheria was twenty times less liable to contract diphtheria again than the average Schick positive reactor, and six times less liable to attack than an average member of the school population. Therefore an attack of clinical diphtheria generally confers a strong degree of immunity, and for this reason it seems easier to explain the majority of the Schick positive reactions of diphtheria convalescents on the theory of primary and secondary stimuli than on the hypothesis of a hereditary defect in the antitoxin forming mechanism, though it is possible such a defect may account for 5 or 10 per cent. of post-diphtheria susceptible reactions.

15. *The Schick Test and Passive Immunity.*

The administration of therapeutic antitoxin inhibits the Schick reaction, and this fact has been used to estimate the duration of passive immunity. Many observations by this means confirm the older work done by actual titration of the antitoxin content of the blood. Passive immunity, sufficient to prevent the reappearance of a positive Schick reaction lasts a variable time according to the dose of administered antitoxin. Park and Zingher (58) state that 1,000 units will generally inhibit the Schick test of a normal child from 21–25 days, but they also make the interesting observation, that if the subject has had a previous injection of antitoxin, the duration of the passive immunity which is conferred by 1,000 units becomes shortened to about ten days. Also in a case of diphtheria the same dose of antitoxin is excreted, or destroyed, quicker than in an uninfected subject.

The Schick test has been used by Lesne and his collaborators (59) to show at what time after injection sufficient antitoxin to inhibit the reaction appears in the blood. The time was found to be about 80 minutes after a subcutaneous, and 50 after an intramuscular, injection. These authors also confirmed the fact that antitoxin administered *per rectum* or *per os* is not absorbed, at least in sufficient amount to inhibit a Schick reaction. Dickenson (10) has noted that an injection of antitoxin after a positive Schick reaction has appeared does not affect its development: a useful practical point, because a specific Schick test can still be distinguished from a pseudo-Schick reaction even if antitoxin has been given a few hours after its first appearance. The heavy percentage of pseudo-reactions seen in diphtheria convalescents has sometimes been attributed to the therapeutic antitoxin. But since the pseudo-reaction is nothing like any serum reactions, and occurs with almost as great a frequency in mild cases, and diphtheria carriers, I think very few pseudo-reactions can be attributed to this cause.

16. *The Schick Reaction in Diphtheria Carriers.*

'The carrier of virulent diphtheria bacilli always has a Schick negative reaction.' This aphorism, while not strictly true, has so few exceptions that it can be acted on for practical administrative work in preventive medicine. That is to say, if a carrier of 'K.L.B.' is known to have a positive Schick reaction, there is no need to test the organism for virulence, or segregate the carrier. Because those organisms, which resemble diphtheria bacilli in smears, or cultures, from the throats of positive Schick reactors, who are not ill, will almost invariably be found to be avirulent if tested on a guinea-pig. The carrier of virulent bacilli must have some sort of immunity, or else he would show signs of disease, and therefore his Schick reaction is almost invariably negative. Those who harbour toxigenic organisms generally have a larger amount of antitoxin in their blood than usual. Zoeller (60) states that whereas the average Schick immune

has about 0·1 unit, the carrier usually has 2 to 3 units of antitoxin per c.c. of blood. The diphtheria carrier state, in combination with a Schick positive reaction, is often mentioned in the literature; but unless the throat swab and Schick test are taken together at the same time, and the organism has been tested for virulence, these reports mean nothing. However, virulent carriers undoubtedly are to be found who have insufficient circulatory antitoxin to inhibit a Schick positive reaction. Harries (27) reported six carriers of virulent bacilli who had positive Schick tests when first seen. One was retested a week later and four were retested within a fortnight of their first test. All these five carriers were found to have become negative reactors in the interval between the two tests. The final case was faintly positive sixteen days after discovery, but definitely negative on the twenty-first day. I have formed virulent cultures out of thirty-six strains of *C. diphtheriae* which had been isolated from Schick positive reactors in whom the Schick reaction was again found to be positive at a retest after the 'carried' bacillus had been proved to be virulent to guinea-pigs. In other cases, boys whose reactions were known to be positive a short time previous to their discovery as virulent carriers, have always been found to be negative reactors at a subsequent retest. Thus, carriers of virulent diphtheria bacilli, with antitoxin in their blood below Schick level, do exist and must be a great deal more common than imagined. Harries' (27) observations show the reason for their rarity is, that if a boy is a Schick positive reactor and becomes a carrier he either responds within a few days by making enough antitoxin to become Schick immune, or becomes a case of diphtheria. It would almost seem as if there was a definite struggle between the human defences and the infecting organisms, the result of which hangs in the balance for some days before either antitoxic immunity is acquired or clinical diphtheria declares itself. In one instance virulent bacilli were obtained from a Schick positive reactor whose throat appeared normal at the time the swab was taken, but seven days later the boy developed clinical diphtheria. This boy was a real 'precocious' or incubation carrier, and for seven days it was doubtful whether he would become immune, without symptoms, or succumb to diphtheria. Therefore, unless the swab and the Schick test synchronize with the first onset of the carrier state the Schick test will be negative. In such observations as these, the antigenic stimulus of the first Schick test may often be the cause of the negative result of the second test; but that does not invalidate the argument, that infection with virulent diphtheria bacilli produces either a basal, or definite Schick, immunity so rapidly as to make the discovery of Schick positive carriers a rare event. The Schick tests of the carriers of the non-toxigenic strain of *C. diphtheriae* may be either positive or negative; but it is rather interesting to note that, in my experience, the incidence of the avirulent carrier state is just twice as high in positive, as in negative, Schick reactors. This observation suggests that immunity to the toxin of virulent diphtheria bacilli is accompanied by an increase in the individual's resistance to infection by the non-toxigenic variety of the species *C. diphtheriae.*

17. *Congenital Schick Immunity.*

The fact that the blood of the new-born infant nearly always contained enough natural diphtheria antitoxin to produce a negative Schick test was one of the earliest observations on human diphtheria antitoxin. With very few exceptions, the blood of the mother, and the cord blood of the infant, show the same amount of antitoxin. More rarely the Schick reaction of mother and infant are different, because, for some unknown reason, the maternal antitoxin has failed to pass the placenta. For instance, von Gröer and Kasowitz (61) found that in only 6 infants out of 143 (i.e. 4 per cent.) was the agreement between the maternal and infantile blood, as regards presence or absence of antitoxin, incomplete. Antitoxin, but in a much lower concentration, also appears in human milk, and Salge (62) showed that the amount of diphtheria antitoxin in the blood of an infant could be increased if it was suckled by a nurse with a high antitoxin titre. For though heterogeneous diphtheria antitoxin is not absorbed by the infantile mucosa, antitoxin incorporated with the mother's milk is. The congenital immunity of the new born is only a passive immunity and fades rapidly during the first year of life. In an ordinary town population the infants are born about 85 per cent. Schick negative, which is the ordinary Schick immunity of the adult female population. At about six months of age Zingher (15) says, that about 40 per cent., and at the end of the first year of life, only 10 per cent., of the infantile population in New York give negative Schick tests. After the age of one, the population begins to slowly regain immunity. The actual loss of congenital immunity is really more rapid than these figures indicate; since the percentage of infants with negative Schick reactions never falls to zero, and the loss of maternal immunity in a population is overlapped by the gain in acquired active-antitoxic immunity. Also the loss of congenital immunity is delayed by breast feeding. Von Gröer and Kasowitz (63) showed that about half the breast-fed babies which they tested still contained an appreciable amount of diphtheria antitoxin in their blood at the end of the first year of life, but in only one-fifth of the bottle-fed babies of the same age was any antitoxin detected by the Römer technique. The high Schick immunity of new-born infants has explained the well-established clinical fact that diphtheria in infants is rare and atypical. The immunity of the new born is also seen in many other microbic conditions and is an interesting example of the adaptation of a species to its environment. The mother, by contact with the common bacteria in her habitat, acquires an active immunity towards them, which is passively transferred to the foetus via the placenta, and to the suckling via the breast. In this way the new-born mammal is passively protected from the pathogenic bacteria in its environment until such time as it acquires an active immunity of its own.

18. *Latent Immunization.*

In 1919 von Gröer and Kasowitz (63) examined the blood-sera of 1,062 of the inhabitants of Vienna by means of Römer's technique, and thus produced the first curve which showed clearly the relationship between age and human circulating diphtheria antitoxin. The Viennese graph was soon followed by similar curves from America obtained by the use of the Schick test. The American and Viennese curves did not exactly correspond and, because it was commonly believed natural antitoxic immunity was a physiological function of age, attempts were made to explain the incongruence of these curves of age and antitoxic immunity cases, as due to pseudo-Schick reactions, or to variable technique, rather than to unrecognized subclinical infections with diphtheria bacilli. One of the most important recent medical advances, which has been almost entirely due to Schick's reaction, is the general acceptance of the theory that immunity to diphtheria, and many other infectious diseases, may be acquired latently without any recognizable clinical symptoms. This theory has shed such a flood of light on many obscure epidemiological phenomena that it is worth discussing in some detail.

Zingher (15) produced many tables of Schick tests from schools, and pointed out how Schick immunity varied according to the social level of the school (see Fig. 3). In the poorest districts of New York the percentage of positive Schick reactors among the children was sometimes less than 30, whereas in some of the better-class schools, with the same frequency distribution as regards age, there were 60 per cent. of susceptible Schick reactors. O'Brien (64) has also demonstrated the same relationship between social conditions and Schick immunity in England. He found, for example, that 64 per cent. of medical students were Schick positive, in contrast to 38 per cent. of children in institutions, and this was so, in spite of the fact that the average age of the students must have been twice that of the more immune children. Therefore Zingher and O'Brien's work showed that there was some other factor, besides age, at work in the production of antitoxic immunity to diphtheria. Social class, nutrition, and manner of living also cannot, in themselves, have much influence in determining the degree of herd immunity in a population group, because, at Greenwich Hospital School, where all these factors remained constant, the Schick positive reactors in 1922 only accounted for 14 per cent. of the school population, while in 1928 this percentage was 27. Again, overcrowding in itself cannot be a cause of a low percentage of susceptibles because a sample of 103 naval ratings, who had lived many years in the cramped conditions inseparable from life at sea, were 36 per cent. positive reactors, and therefore on the whole these seamen were less Schick immune than less dense adult population ashore. O'Brien (65) tested the boys in a mercantile training ship just after the outbreak of a diphtheria epidemic, and found that 84 per cent. of them had negative Schick reactions. He also tested the newly joined boys who had not been through the diphtheria outbreak, and found that they were only 57 per cent. immune. Taken together, these observations,

almost without any additional explanation, enunciate the hypothesis that the diphtheria antitoxin in the human circulation is acquired by contact with diphtheria bacilli. And, except as factors which increase or diminish the closeness of this contact between bacteria and man, age, race, social condition, or nutrition, have in themselves a very little influence on natural antitoxic immunity. Wassermann (66), I believe, first suggested that natural human antitoxin was an acquired

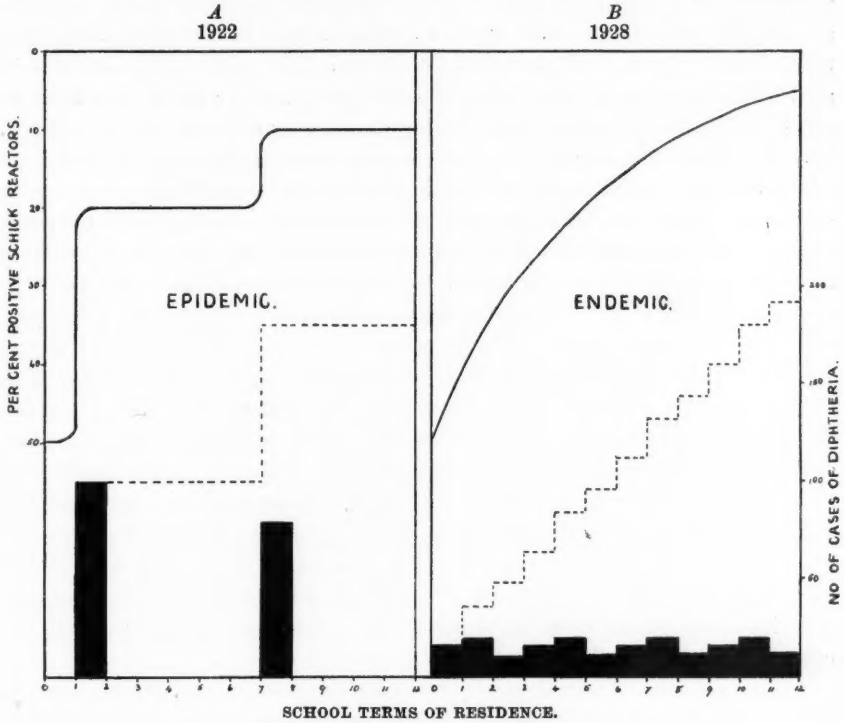


FIG. 1. Schick Immunity.
Continuous lines represent increase of Schick immunity.
Dotted " " " " diphtheria experience.
Black columns = diphtheria incidence.

character, the result of antigenic stimuli from subclinical infection with diphtheria bacilli. However, the theory received little attention until the results of massed Schick testing produced such overwhelming evidence in favour of this hypothesis.

The continuous series of observations made during the last eight years at Greenwich school put the hypothesis of latent immunization beyond any reasonable doubt, therefore a very brief sketch of this work will be given.

Fig. 1 gives two diagrams which are founded on the Schick tests of the boys who were inhabiting Greenwich Hospital School in January 1922 and January 1928. During the interval between these dates the entire population had changed, therefore these two series of Schick reactions included no retests. In order to simplify the demonstration, Fig. 1 has been made purely diagrammatic.

The actual Schick and morbidity statistics on which these diagrams are based have been published elsewhere (67, 68). In both diagrams the boys of the school have been arranged in thirteen groups, each group consisted of a school term's entry. These groups are arranged from 0, which represents the new boys who entered the school, during the term that all the boys were tested, to 12 which represent the most senior group of boys who had been twelve terms in the school at the time of testing. The black rectangles along the base lines of the diagrams are roughly proportional to the number of cases notified in each of the terms that the most senior group of boys were in residence. The height of the dotted lines above the base line at any point is equivalent to the sum of the cases of diphtheria which had accumulated during the number of terms indicated below. Thus the dotted line is an index of the relative opportunities each group of boys who had been in residence for a different time had had of coming in contact with diphtheria cases. In the same way the continuous lines in both diagrams represent the percentage of Schick negative reactors in each group who had been a different number of terms at school. In the 1922 series of tests with the boys thus arranged in order of seniority, the new entries were 50 per cent. immune, boys who had been two to seven terms at school were 80 per cent. immune, while those who had been more than seven terms at school were 95 per cent. Schick negative reactors. Thus there were two abrupt steps in immunity. The chart shows that each of these steps took place immediately over the two big outbreaks of diphtheria which had occurred one, and seven, terms before that term in which all the boys were Schick tested. Since there was no diphtheria incidence between these two epidemics, those boys who had been in the school six terms were no more immune than the second-term boys, because both had only experienced the one epidemic of diphtheria, whereas all the groups of boys who had been seven or more terms in the school had passed through two epedemics, and were all equally more immune.

The 1928 series of tests showed quite a different phenomenon. The chart shows that diphtheria had been endemic, and had occurred each term for the previous three years; therefore experience of diphtheria increased gradually term by term, not in two abrupt steps, and similarly the Schick immunity of the seniority groups increased in a smooth curve instead of in two sudden steps.

I do not think it is possible to produce a prettier demonstration than this contrast between the 1922 and 1928 Schick tests, that antitoxic immunity is a function of previous experience of diphtheria. These diagrams, as drawn, also show that during each period of three years, prior to the two series of tests, there were about the same number of diphtheria cases. In the earlier period the cases were distributed in two epidemics. In the later period the diphtheria cases were more or less evenly spread throughout the three years. In both periods the resulting amount of herd immunity acquired by the most senior group of boys was about the same, because, both in 1922 and 1928, the most senior group in each series had had about the same amount of experience of diphtheria bacilli, the first in two large doses, the second in thirteen small ones. In these

diagrams the boys are represented according to their seniority in the school, not according to their age. Owing to a fairly wide range in the age on entry, it was possible to pick out from the boys used for the 1928 series of tests those boys who, although they were over 14 years of age, yet had been less than a year at school, this group contained 35 per cent. of positive Schick reactors in contrast with 18 per cent. among the boys of over a year's residence, but under 14 years of age. That is to say 'Young seniors' were more immune than 'Old juniors' (68).

Therefore the increase of herd immunity with age is due, not to a physiological function of age itself, but to the fact that, on the average, the older any one is the more opportunities he will have had of receiving antigenic stimuli from the bacteria in his environment.

19. *The Mechanism of Latent Immunization.*

The exact mechanism by which human beings acquire diphtheria antitoxin in their blood, without obvious clinical symptoms, is still far from certain. Lereboullet (69) has confirmed the Greenwich observations on a much younger age group in a children's hospital in Paris. He found age to be of secondary importance in determining the degree of immunity of a group. There were more negative reactors in his sample of 2 to 5 than of 5 to 6 years of age, and no child who had been over twelve months in hospital had a positive Schick reaction. He attributed latent immunization (*L'immunization spontanée occulte*) to slight catarrhs and sore throats which pass unrecognized as diphtheria, except during an epidemic. I assume these subclinical missed cases scarcely differ in degree from the ordinary contact carrier, who frequently has a normal-looking throat and no catarrh whatever. If actual infection as a carrier is necessary to stimulate circulatory antitoxin there are always more than enough carriers to account for all the Schick immunity produced each year. According to Forbes (70) the virulent carrier rate during recent years has rarely fallen below 2 per cent. in the London County Council Schools. According to the work of Martin and Hartley (71) and Weaver (72) it would seem that the average duration of the diphtheria carrier state can scarcely exceed twenty-four days. Such a duration of 'carrying' implies that 30 per cent. of the population could be infected during one year, which means every child has the chance of becoming a carrier three times between the age of 5 and 15: the period of school life. Perhaps actual infection, even as a mild case or carrier, is not essential to stimulate Schick immunity. The observations of Monkton Copeman (73), Monmignant (74), and many others, have proved that Schick immunity can be produced by spraying the throat with toxin-antitoxin mixture, or by instilling 'anatoxin' into the nose, just as easily as by means of hypodermic injections of a diphtheria antigen. Since this is so, latent immunization may sometimes be caused, without any definite infection, by the mere destruction and absorption of living, or dead, diphtheria bacilli, or even of their products in the atmospheric

dust, i.e. by a process of 'natural autovaccination'. In the succeeding paragraphs the term 'latent immunization' will be applied to immunity which is acquired without recognized symptoms; 'natural immunization' includes this immunity with that which may have been conferred by a definite clinical attack of diphtheria.

20. *The Rate of Natural Immunization.*

The hypothesis of natural and latent immunization explains all the difficulties in the distribution of Schick immunity, relative to age, at different times and places. Among the well-to-do classes the chances of contact with diphtheria are considerably less than in the poor densely populated districts of big towns. Therefore Schick immunity increases with age at a quicker rate in the towns than in the country, among the poor than among the rich, and in institutions than in private houses. In short, *given the presence of diphtheria bacilli*, the type of the environment determines the intensity of the antigenic or immunizing stimuli. This intensity can be measured by calculating the rate at which the positive Schick reactions in any community change to negative. The relationship between the rate at which human circulating diphtheria antitoxin is acquired, and the type of the environment which a human herd occupies, can be most easily envisaged by the help of a diagram. Fig. 2 is a curve which represents the rate of immunization of an imaginary group of Greenwich naval schoolboys, who were all born at the same time. At birth 15 per cent. of this herd had positive Schick tests. During the next year most of this passive congenital immunity was lost, and the percentage of susceptible reactors rose to 85. By the age of 12, under the influence of the average environment, normal to their class, the group became 50 per cent. immune. The group then all entered Greenwich Hospital School, which had a much denser population of boys and diphtheria bacilli, than the environments in which these new entries had been living for the first twelve years of their life. Therefore the susceptibility of the group declined more rapidly than before, and 50 per cent. of the residual Schick positive reactors became immune during the course of the next two years. At this period the 25 per cent. of the herd, who still had positive Schick reactions, were artificially stimulated with a diphtheria prophylactic. As a result, within four months, the imaginary group of boys became 95 per cent. immune. The rate at which the susceptibles became immune during each period can be calculated by use of one of the formula based on the 'compound interest law'. Up to 12 years of age the rate of immunization was equivalent to 1·8 per cent. of the residual positive Schick reactions to become negative every four months (i.e. a school term). In the residential school the rate was 12 per cent. per term. The inoculation with diphtheria toxoid accelerated this rate to over 80. Thus the relative intensities of the antigenic stimuli, of the ordinary environment, of the residential institution, and of diphtheria toxoid, were about as 1 is to 7 is to 50 (or 1 : 7 : 50). These figures demonstrate the superiority of the artificial, over the natural, means of producing circulating diphtheria antitoxin. Natural and latent immunization are

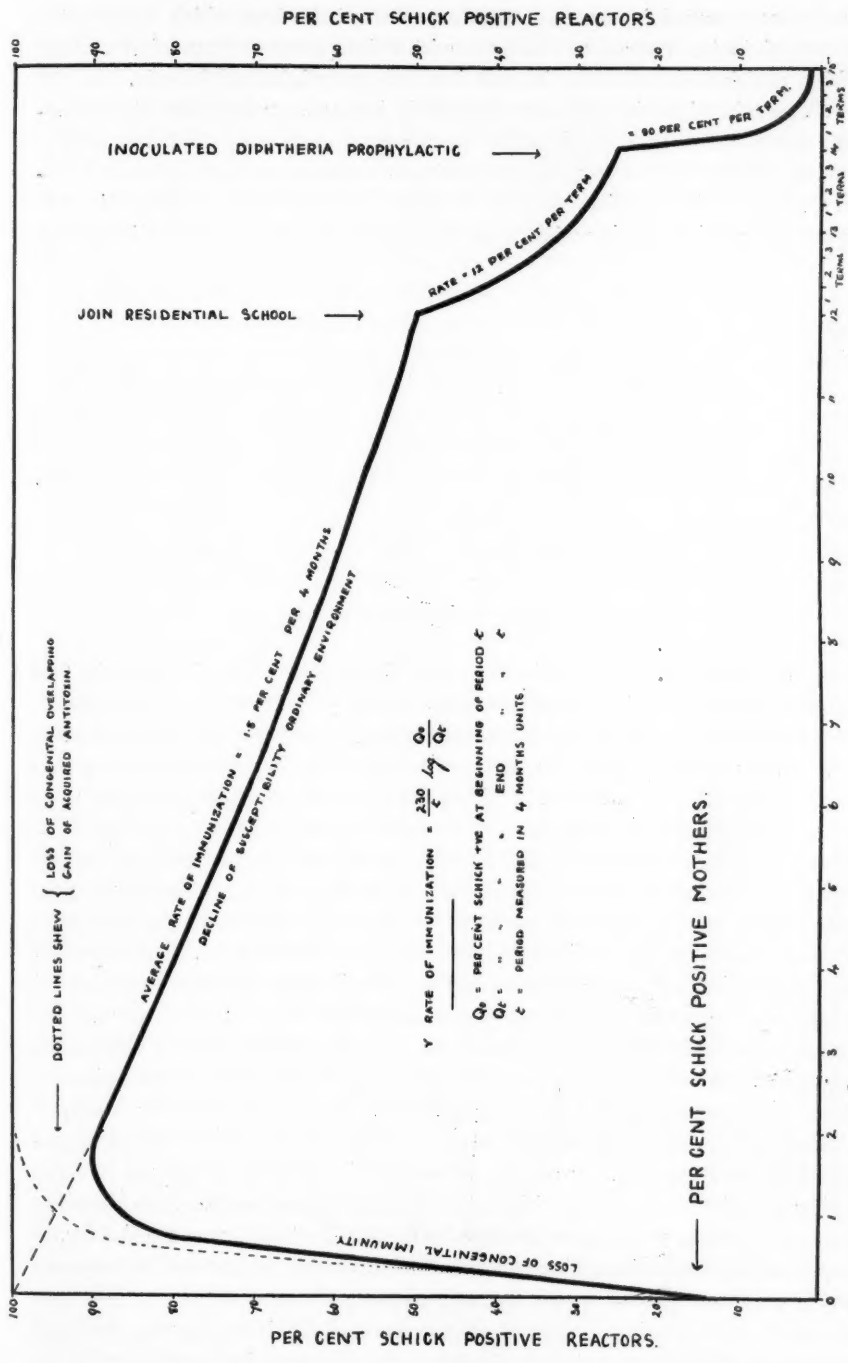


Fig. 2. Schick Susceptibility. Rate of Immunization in a Hypothetical Herd of Boys.

always accompanied by a certain number of case infections which varies with the rate of the immunization. In Greenwich School about one out of every four Schick positive reactors who became immune got clinical diphtheria. In the L.C.C. schools this ratio would have probably been nearer one case with symptoms to ten latent immunizations, but there are not sufficient Schick test data of London school children to make this estimate much more than a guess. However, Frost (75) has published a most illuminating paper on the epidemiology of diphtheria in Baltimore, in which he has calculated the price of natural immunity

TABLE I

Column	*a*	*b*	*c*	*d*	*e*	*f*	*g*
Age Group.	Rate per 10,000 of Whole Group.		Ratio of *a* : *b*.	Rate of Immunization.		Schick Positive Range of Age Group.	Diphtheria Morbidity per 10,000 Residual Schick Positives.
	To become Schick Immune.	To get Clinical Diphtheria.		Of Whole Group.	Of Residual Schick Positives.		
Under 5	430	96	4·5 : 1	4·3	5	100–78	110
5–10	610	86	7·1 : 1	6·1	9	78–48	140
10–15	320	21	15·2 : 1	3·2	8	48–32	50
0–15	453	69	6·6 : 1	4·5	7·6	100–32	140

Diphtheria in Baltimore (modified from Frost (75)).

in diphtheria cases. Table I is expanded from one in Frost's paper by the addition of the four right-hand columns. This table shows that the ratio of those to become naturally immune to those who got diphtheria increased with age. Under the age of five this ratio was a third of what it became in the group between 10 and 15 years old. This is what would be expected if the most susceptible subjects get weeded out of the Schick positive group early in life by getting diphtheria and becoming immune later, and if the residual Schick positive reactors continue to increase their immunity, while still Schick positive, before finally changing their reaction to negative. According to the rates of immunization of the population used by Frost (Table I col. *d*) the speed of acquiring antitoxin is not greater during the school age period than in pre-school life, this is because the rates in col. *d* were calculated as percentages per annum at simple interest of the whole population, including all Schick negative reactors. Column *e* in Table I, calculated from column *f*, gives the rates of immunization limited to the susceptibles in the population. It is seen that this index, of intensity of the antigenic stimuli in the environment, increased from 5 in pre-school life to 9 per cent. per annum of susceptible reactors to become immune during the school age period. This seems a more logical result. Also since the chances of coming in contact with diphtheria bacilli must be very similar for all ages at school, little diminution in the rate of immunization would be expected during the latter half of school life, and column *e* shows that actually such was the case. It is seen from column *b*, that as is usual, the 1–5 age group produced the highest diphtheria morbidity. At first sight, this seems incompatible with the

statement that the intensity of the immunizing influences was greater during the school than the pre-school age period, as indicated by the rates of immunization given in column *e*. But if the diphtheria morbidity is calculated per 10,000 residual Schick positive reactors as in column *g*, instead of per 10,000 of the whole group as in column *b*, there is a significant rise in morbidity during early school life, which falls off in the latter period as the Schick susceptibles increase their immunity to diphtheria. That this is a correct interpretation of the figures is further suggested by the fact that the rise in the morbidity of the Schick susceptibles from 110 in pre-school to 140 in early school life is not directly proportional to the corresponding acceleration of the rate of immunization, from 5 to 9 (col. *e*).

The use of only the Schick positive, instead of all members of a population group, on which to calculate the morbidity and rate of immunization, makes the whole process of natural immunization more comprehensible. The whole of Frost's paper is a most valuable confirmation of the hypothesis, that immunity to diphtheria among the Schick positive reactors of a community may steadily increase with experience long before the Schick reaction itself becomes negative (vide section 12).

The significance of the variations in the age incidence curves of Schick immunity becomes clearer in the light of the foregoing paragraphs, and in Fig. 3 I have specially selected a set of these graphs in order to demonstrate their great variability and some other points of interest. The authors from whose statistics the curves in Fig. 3 were plotted are indicated below it. The 'New York infants' and the German curve start early enough in life to show the primary increase in susceptibility as the antitoxin acquired from the babies' mothers was lost. The three other New York curves are from three grades of schools and illustrate well the difference in Schick immunity, caused by the social conditions of the poorer environments leading to closer contact between the members of the herd. The variation in the intensity of the antigenic stimuli in the three schools is indicated by the different rates of immunization being 3, 8, and 12 per cent. of susceptibles per annum to become Schick immune. When immunization rates are deduced from these age curves it is assumed that the eldest group, when it was the same age as the youngest group, had had the same degree of immunity as the youngest age group had at the time when both groups were Schick tested. This is really an unwarrantable assumption, unless it is known that, previous to Schick testing, the immunizing influences at work had remained constant during a number of years, equal to the difference between the ages of the oldest and youngest groups: as in the 1928 Greenwich curve (B. Fig. 1). Unfortunately in very few reports are the exact dates of the Schick tests and the incidence of diphtheria in the district, during the whole lifetime of the oldest age group, ever given. This data is essential in order to properly correlate Schick immunity with diphtherial experience. For this reason it would probably have been more scientific to have calculated the average immunizing rate from birth for each age group, on the assumption, which is probably true, that every group was born with no acquired natural active immunity (maternal

passive immunity can be ignored); but such a method would have been more laborious, and less useful for demonstration purposes. In the case of the New York curves, the antigenic stimuli were probably much the same from year to year, since diphtheria of recent times has been endemic in New York and the morbidity has averaged about 25 per 10,000 per annum. In this connexion the Aberdeen curve is rather paradoxical because, although the diphtheria morbidity was about the same as in New York, yet as Fig. 3 shows the Schick susceptibility of the Aberdeen sample was high. But the sample was relatively small and included a large group of better class children. The peculiar shape of the German curve, which is plotted from Birk's statistics which were criticized in section 10, if not due to unreliable Schick toxin, could be accounted for on the pure assumption that diphtheria had been prevalent in Tubingen eight years before the time the Schick tests were done, but had then disappeared from the district only to reappear again just prior to the period of the Schick testing. The first prevalence of diphtheria would have given the children of over 8 years old a higher degree of Schick immunity than those under 8, as Fig. 3 indicates, while the second prevalence would have caused the susceptibility of all age groups to decline equally and thus account for the lack of any difference in the immunity of children over 5 and infants 1 year old, who all show, according to Fig. 3, the same degree of Schick immunity; which degree is high for their average age. If this romance was true, the Tubingen curve would be the analogue of the 1922 Greenwich curve (Fig. 1 A). The two groups in Fig. 1 were purposely 'idealized' in order to make the main principles of natural immunization easier to envisage, and, if their significance is thoroughly grasped, all the vagaries of 'Schick immunity and age' curves, which are illustrated by Fig. 3, are at once seen as the history of the prevalence and intensity of diphtheria infection in the environment during the lifetime of the oldest age group.

21. *The Schick Test and Artificial Immunization.*

It is not considered part of this essay to discuss the many metabolic products of the diphtheria bacillus, which have been used to stimulate artificially the production of human circulatory antitoxin, but it is not out of place to point out that the success of active immunization in diphtheria is entirely due to the Schick test. The fact, that it is possible to see if an inoculation has proved successful in provoking an active immunity, is of inestimable advantage. By means of such a test it is easy to discover which subjects require longer and more intensive courses than usual, to explain why an inoculated individual contracted the disease he was supposed to have been protected against, and to find out what intervals between inoculations produce the best results. The Schick reaction may be said to have proved that the administration of any vaccine prophylactic, without the control afforded by an immunity test, is a mere shot in the dark. As long ago as 1909, Theobald Smith (76) demonstrated that diphtheria toxin, which had been neutralized with diphtheria antitoxin, could

produce an active immunity in guinea-pigs, and that this immunity lasted over several years. At the time Theobald Smith said, 'The method therefore invites further tests in regard to its ultimate applicability to human beings'. Park (1913) (77) should get the credit of first describing the manufacture of, and popularizing the use of, toxin-antitoxin mixtures for the prevention of diphtheria. More recently Ramon (78) in 1923 showed that if diphtheria toxin was heated at 42° C. in the presence of about 0·3 per cent. of formaldehyde it loses its poisonous character, but retains its immunizing property. The prophylactic thus produced is Ramon's 'anatoxin', which has been used extensively in France during the last few years. Various modified, non-poisonous products of diphtheria toxin are rapidly supplanting the older toxin-antitoxin mixtures, since these newer preparations avoid any chance of accident due to free or excess of toxin in the prophylactic, and remove the objection that the antitoxin (i. e. horse serum) may render a subject anaphylactic. One of the most modern diphtheria prophylactics is that described by Glenny and Pope (1927) (79) as diphtheria 'Toxoid-Antitoxin Floccules'. This product, which in my experience is a better immunizer than ordinary toxoid, has the advantage of containing only about 1/50 of the amount of superfluous nitrogenous matter which encumbers the older prophylactics. As a result, when this product is used, the painful local and constitutional reactions, which were by no means infrequent with the older antigens, entirely disappear. As previously mentioned, active immunization can also be produced by the application of diphtheria prophylactics to the nasal and tonsillar mucus membranes, and Pockels' (80) claims to have produced antitoxic immunity by the mouth by giving children emulsions of dead diphtheria bacilli to drink, though generally of a degree below the Schick level. Zoeller and Ramon (81) and others have failed to confirm Pockels' work. All the above progress would have been scarcely possible without the control of a simple immunity test such as Schick's reaction. By the use of the Schick reaction, and working on Glenny's principle of primary and secondary stimuli, the best spacing of prophylactic inoculations for producing the most efficient results is gradually being learnt. As mentioned in section 11, O'Brien (46) found that the Schick test itself is an efficient secondary antigenic stimulus in sensitive Schick positive subjects, and for this reason Parish and O'Kell (38) have quite rightly pointed out that estimations, of the immunizing influences of an environment based on retesting population groups at intervals, must be carefully criticized. A good deal of work of this description has been done at Greenwich; and I have come to the conclusion that the change in the immunity, which repeated Schick tests indicated had taken place in the interval between tests and retests, was in some cases more than it was legitimate to ascribe to natural environmental stimuli. If such was the case, some of the immunity was doubtless caused by the previous Schick tests themselves having acted as secondary stimuli. This opinion was formed, because the increase in the percentage of negative reactors found by retesting the same groups of boys at different times, was on the whole greater, than the increments of herd immunity which were

indicated by the indirect method of testing groups of differing seniority at the same time in the way described in section 18. Parish and O'Kell's warning does not of course apply to the latter method. However, the differences, due to the artificial antigenic stimuli of the previous Schick tests, could not have been large enough to violate any conclusions which had been drawn from them concerning the natural antigenic influences of the Greenwich school environment.

22. *The Rate of Artificial Active-Immunization.*

Zingher (82) was one of the first authorities to point out that when the Schick positive reactors of any community were inoculated with a diphtheria prophylactic, the higher the percentage of natural Schick negative reactors, in the community, the quicker and easier it was to immunize artificially the Schick positive members of that community. For example, in one school which contained originally 80 per cent. of natural negative reactors, half of the 20 per cent. of positive reactors became negative during the same time, and with the same doses of prophylactic, which were only able to immunize a quarter of the 50 per cent. of the Schick susceptibles in a school where the original number of those naturally Schick immune was 50 per cent. This phenomenon, which is now accepted as a general rule, is a natural corollary to the hypothesis of natural latent immunization, because the percentage of negative Schick reactors in any population group is an index of its past experience of diphtheria. Therefore the Schick positive reactors, in a group containing many Schick immunes, will have had more experience of diphtheria bacilli than the Schick positive reactors from a group which includes few Schick immunes. Hence the susceptibles from the more immune population will be more sensitive to antigenic stimuli than the Schick positive reactors from a community which has had less exposure to diphtheria bacilli.

Just recently, the opportunity arose at Greenwich to test the truth of this hypothesis more directly (68). Three sets of boys who were comparable as regards age, social class, and race, and who were at the time living under exactly the same environmental conditions were inoculated with diphtheria prophylactics. The only significant difference between the three groups was the time that they had been exposed to the influence of the school environment, where the opportunities of diphtherial infection of recent years, as judged by diphtheria incidence, were seven times as great as those in the London County Council Schools. The first group, who had been less than one term in the school, became immune at a rate equivalent to 30 per cent. of residual susceptibles per month. The second group, consisting of boys who had been less than one year (i. e. three terms) in school, became immune at 42 per cent. per month. The third, and most senior group, with over a year's residence, was immunized at the rate of 60 per cent. per month. There were 32 per cent. of original immunes in the first, 64 per cent. in the second, and 84 per cent. in the third, and most senior, sample.

Hence the relative proportions of negative reactors in the groups at the beginning of the prophylactic course was roughly 1 : 2 : 3, while the relative rate at which the susceptibles became immune was roughly 2 : 3 : 4. Therefore the Schick positive reactors, who had over a year's experience of the diphtheria bacilli in the school atmosphere, became Schick negative reactors twice as fast as the group of new entries to the school who had had no such experience.

I think the preceding sections justify the following conclusions :

1. Immunity to diphtheria is more often gained latently than by a definite clinical attack.

2. The amount and rate of immunity gained by a population group depends more on the duration and intensity of the diphtheria prevalence in the environment, than on a physiological function of age itself, or on the hereditary qualities of the population.

3. Active immunization of the susceptibles in a community by artificial means is easier the greater the proportion of immunes originally present; because the Schick positive reactors in the community will have had more opportunity of contact with diphtheria bacilli, which will have sensitized them to further antigenic stimuli, even though their previous bacterial experience had been insufficient to raise the antitoxin content of their blood to above Schick level (0·03 unit per c.c.).

23. *Sex and Schick Immunity.*

In all the Schick statistics which I have seen, where the data for the sexes has been given separately, the percentage of positive reactions is always greater in the female than in the corresponding male age group. Fig. 3 shows graphs representing male and female Californians which show that, for the period in question, males became immune at twice the rate for females. The Californian totals were, 3,582 females with 60 per cent. of positive reactions, against 50 per cent. of 3,082 males. Zingher, in 1917 (83), in an American institution which had experienced a high diphtheria morbidity, found only 4·1 per cent. of 218 boys but 15·5 per cent. of 148 girls had positive Schick reactions. A more recent series of Schick tests from Asbury Park, U.S.A. (37), which was performed in 1923 and 1924 on some 1,200 children in which the sexes were about equally divided, gave a 74 per cent. female and 62 per cent. male Schick susceptibility. Outside the United States the same preponderance of female Schick positive reactors is also to be found. In Holland Bessemans (84) found 46 per cent. of the girls and 41 per cent. of the boys susceptible reactors, while in another province Lomry and Dublé (85) found 49 per cent. of females to 41 per cent. of males Schick positive reactors. Smits (86) reported 8 per cent. of 200 females but only 2 per cent. of 300 men in Sumatra gave positive reactions ; and in the Philippines Gomez, Navarro, and Kapaun (87) state the percentages for females and males are 14 and 6 respectively. Therefore the tendency of females to be more Schick susceptible than males seems widespread throughout the world,

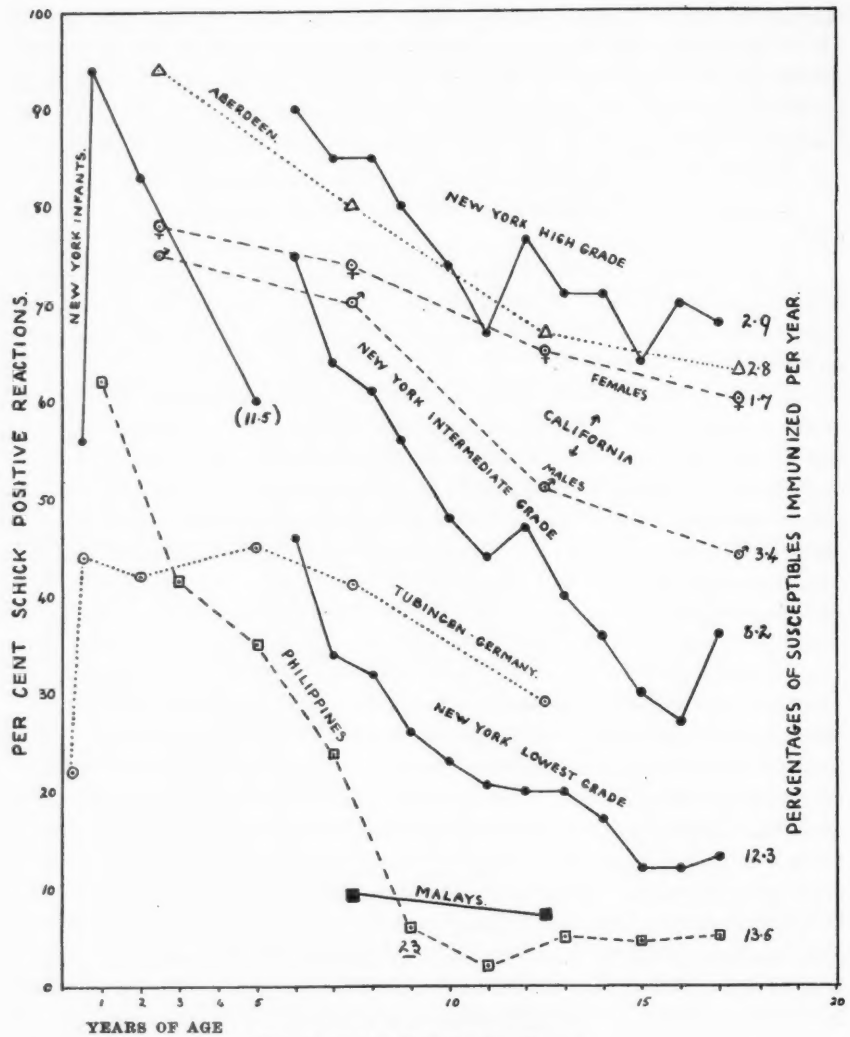


FIG. 3. Schick Tests by Age Groups.

Place.	*Author and Reference.*	*No. in Sample.*
New York	Zingher (15)	150,000
California	Kelly, Stevens, and Beattie (14)	6,000
Aberdeen	Kinloch, Smith, and Taylor (33)	1,500
Tubingen	Schwalbe (42)	?
Philippines	Gomez, Navarro, and Kapaun (87)	1,030
Malays	Fletcher (89)	172

The figures at the ends of the graphs give the rate of immunization between the highest and lowest age groups as per cent. susceptibles per year becoming immune.

which is of interest in connexion with the long-established clinical observation, that females are more prone to get diphtheria than males. In a Kerr's (88) text-book it is written: 'Females show a greater apparent susceptibility than males, "apparent" because of the greater risk of infection—the females of a family naturally look after the diphtheria cases.' I think that the Schick test has demonstrated that this is not the correct explanation. The incidence of endemic diphtheria is generally greatest where the Schick immunity is highest, since exposure to diphtheria causes more 'latent immunizations' than typical cases.

TABLE II

		Total Numbers. All Ages.	– of Total.	1-4 Years.	Increase between Last and Next Column.	5-9 Years.	Increase between Last and Next Column.	10-14 Years.	Increase between Last and Next Column.	15-20 Years.	Increase between Last and Next Column.	Over 20 Years.
			%	%	%	%	%	%	%	%	%	%
Schick immunes	Male	3082	50	23	11	32	24	49	19	59	31	71
	Female	3582	40	21	8	28	10	35	10	41	22	54
Ratio ♂/♀		—	1·3	1·1	1·4	1·1	2·4	1·4	1·9	1·4	1·4	1·3
Protein reactors	Male	3082	22	1·5	5	6·9	12	18	11	27	22	43
	Female	3582	17	1·2	7	8·1	7	14	6	19	12	29
Ratio ♂/♀		—	1·3	1·3	0·7	0·9	1·7	1·3	1·8	1·4	1·8	1·8

Age	Under 20.									Over 20.		
	Total Group.			– Reactors.			+ Reactors.			667 Males. 1027 Females. Per cent. ψ		
	No. in Sample.	No ψ.	% ψ.	No. in Sample.	No ψ and –.	% ψ.	No. in Sample.	No ψ and +.	% ψ.	Of Total Group.	Of –	Of +
Males (♂)	2415	385	16	1042	284	27	1373	101	7·4	43	51	23
Females (♀)	2555	319	13	897	227	26	1658	92	5·5	29	39	17

ψ = protein or pseudo-reaction. – = negative. + = positive, Schick.

Analysis showing the relationship between Schick immunity and *allergie*, and sex and age, in California.

From details in Kelly, Stevens, and Beattie's report (Ref. no. 14).

For example, in Greenwich Hospital School the Schick herd immunity was much higher than outside, but so was the morbidity. It could be argued, however, that the females in every community, as a rule, lead a more sheltered life than the males; hence females acquire less immunity from their environment, but at exceptional moments in their existence, as when they have to nurse the diphtheria cases in their families, females run greater risks of contracting infection than males. In this way a lower female than male herd immunity could become combined with a higher female than male morbidity, even in places where diphtheria is endemic. There are, however, several deductions which can be made from the most detailed figures in Kelly, Stevens, and Beattie's valuable report (14) that are very much against accepting this explanation. Table II, which is made from the Californian report, gives the percentages

of Schick immunes at five age groups and the percentage increase of immunity between each group of figures which would be equivalent to the rate of immunization for the five years period *between* the mean age of each group.

The table shows that the females acquired circulating antitoxin at a slower rate than the males at all ages. Moreover, at the very ages where one would think the male and female existence was most similar, mainly in the mixed schools of the United States, the ratio of the male to the female rate of acquiring Schick immunity is highest. The response of the males to the antigenic stimuli of school life seems so disproportionately greater than that of the females as to strongly suggest that sex in itself has something to do with the lower Schick immunity of the females. The same report gives the Schick reactions separately for the sexes in the Sonoma state home for mental defectives. The age-distribution is practically the same for both sexes, and the inmates of this home are about 50 per cent. more Schick immune than the non-institutional population of California; therefore it can be assumed that most of the Schick immunity of its inhabitants was gained while they were in the institution. An assumption that becomes more legitimate when it is definitely stated in the report itself that repeated epidemics of diphtheria had recently occurred in the Sonoma home. Again, in an institution of this type the male and female inhabitants must have been living under conditions more alike than elsewhere, but the difference in susceptibility is just as marked as usual, because there were 27 per cent. of female to 18 per cent. of male positive Schick reactors. All of which tends to suggest that sex itself was the differential factor which was responsible for the excess of female over male susceptibility. The evidence on the whole seems to favour the hypothesis that the potentiality of responding to antigenic stimuli from the diphtheria bacilli in the environment is greater in the average male than the average female. If this is so, susceptibility to diphtheria is, to some extent, a real hereditary sex-linked character.

The California report shows one or two interesting points as regards sex and pseudo-Schick reactions. Below the Schick immunity figures in Table II, the protein-reaction figures are arranged in exactly the same way; and practically all that has been said about gaining Schick immunity applies equally to acquired *allergie* to diphtheria as indicated by protein reactions. So much is this the case, that one is almost forced to the conclusion that the potentiality to become allergic towards diphtherial protein must also either be a sex-linked character, which is greater in the male than the female, or both *allergie* and antitoxic immunity must depend equally on a difference in the way of life of the sexes. If, however, the protein reactions of susceptible and immune Schick reactors are examined separately a very interesting fact emerges, especially if adults are excluded. Table II (lower section) gives the frequency of protein reactions in susceptible and immune male and female Californians under the age of 20. In the report all adults over 20 form one group and this group is very variable; possibly because it is not a random sample as regards males and females, since

there are nearly double as many females as males over 20, while all the other groups contain about an equal number of both sexes. Also in the United States the sexes live a more or less similar life up to 20, after which the male and female mode of life diverges—more men going out daily to work and more women staying at home all day. This accounts for the preponderance of women in the group over 20, and made it advisable to exclude adults from the analysis of allergie and Schick immunity. When this was done, the percentage of protein reactions among male and female Schick immunes became almost equal—27 per cent. male and 26 per cent. female. The corresponding percentages among the susceptible reactors show a significant difference, being 7·4 per cent. male to 5·5 per cent. female.[2] That is to say, while protein reactions were only 4 per cent. more frequent among male than female negative Schick reactors, 'combined' pseudo- and positive Schick reactors were relatively 35 per cent. more common in the male sex. Now the work at Greenwich has shown that many pseudo-reactions are acquired at the same time as Schick immunity, only to be lost later. This suggests that, in the aggregate, male and female *immune* protein reactors are those groups in the two sexes who have experienced equivalent amounts of antigenic stimuli, otherwise the protein reactions of the sexes would disappear at different rates, and the relative number of immune protein reactors would be different in the two sexes. There would also be a sex difference in the relative numbers of immune protein reactors, if there was a difference in the male and female potentiality to become allergic, unless it is assumed that there is a greater tendency to acquire and retain protein reactions in the female immune Schick reactor, which is exactly counterbalanced by a less exposure of females than males to diphtheria bacilli. The latter is the more complicated hypothesis, and by 'William of Occam's razor' should be discarded in favour of the more simple hypothesis, namely, that there is no sex difference in the protein sensitiveness of Schick immune reactors, and therefore the immune males and females had experienced the same average degree of diphtheria antigenic stimuli. Supposing that males and females, irrespective of their Schick immunity, were all equally sensitive to the stimuli which produce allergic reactions, and that these stimuli are the same that produce Schick immunity, the presumption that the excess of male Schick immunes was due to a genetic sex-linked factor would be very strong. However, the fact that when Schick susceptible reactors are considered there is a relative preponderance of male pseudo-reactions among susceptible reactors has to be accounted for. In sections 4 and 5 it was decided that the protein reaction indicated fairly recent, or intense, diphtherial contacts. If the proportions of pseudo-reactions in Schick immunes had not been equal in the sexes, the obvious explanation would be that males receive more frequent and intense stimuli than females, and therefore they become immune quicker and show more protein reactions, and that sex differences have nothing to do with the question. But if this was true, the females, because they became immune more slowly and therefore showed fewer combined reactions, would in

[2] The difference between the percentages, 1·9, is over three times its probable error, 0·58.

the aggregate, once immune, lose their protein reactions more quickly than the males, since it would be absurd to assume the fact of their becoming immune meant that the whole female population entered a more intense diphtheria environment than they occupied when susceptible. Therefore the fact that combined reactions are more frequent in males than females, while the relative number of pseudo- and negative reactors are equal in both sexes, again suggests that there must be a group of the population who are refractory responders to diphtheria bacilli, both as regards the production of protein sensitiveness, as well as circulatory antitoxin, and that this group contains more females than males.

24. *The Schick Test, Latitude and Race.*

The reports of the Schick testing which have come from the tropics indicate that the natives of low latitudes nearly always possess a much higher degree of Schick immunity than is commonly found among Europeans and North American whites. Gomez and his collaborators (87) give figures for the Philippine Schick immunity which have been plotted in Fig. 3. This curve shows a higher rate of immunization than any other, being 13·5 for the whole period of the graph. Inspection of the Philippine graph also indicates that the population practically acquired all its immunity during the first ten years of life, and as the figures stand, during this period the rate was 23 per cent. of susceptibles per year to become immune. As the result of this rapidity of acquiring circulatory antitoxin, the percentage of positive reactors in the total tested population was only 8·8, since this series of tests contained a high proportion of subjects of over 10 years of age. At the bottom of Fig. 3 are indicated the positive reactors in two age groups, 5–10, 10–15, of Malays as reported by Fletcher (89). The Schick susceptibles in these groups were 9·3 and 7·4 per cent. respectively, which is only equivalent to an immunizing rate of 5·1 ; but perhaps this rather slow rate is explained by analogy with the Philippine curve, and the Malay rate of immunization would have appeared to be much more rapid if a sample had been included from the unexamined age group of 1–5. These Malay samples were also too small for the difference between them to have much significance. Smits (76) says only 5·4 per cent. of 500 adult Javanese had Schick positive reactions, but mentions that 41 per cent. of 100 children were susceptible reactors, which again indicates that in the natives of low latitudes nearly all the immunity of the population is acquired in early life. Taliaffero (90) reports that in Honduras only 10 per cent. of 196 native children as compared with 58 per cent. of 40 white children, both groups aged 5–15, were positive Schick reactors. This report is interesting, as the normal white results control the reliability of the Schick toxin when used in the tropics, and suggests that hot weather, in itself, cannot have much effect in stimulating or accelerating the production of natural antitoxic immunity to diphtheria. Doull (91) and his collaborators report high immunity rates in Brazil, and also note that clinical diphtheria is rare: only 0·8 per cent. of children and adolescents give any history of an attack; whereas

in Baltimore about 10 per cent. of children by the age of 15 had had diphtheria (according to Table I). All other authors who have noted the point remark on the scarcity of clinical diphtheria in the tropical zone, for example, the Philippine diphtheria morbidity is given as 0·2 per 10,000 (1921–25), about one-seventieth the morbidity in England. There are few data concerning the prevalence of carriers in the tropics, but Vardon (92) states that in India the carrier rate for *virulent* diphtheria bacilli may be as high as 3·6 per cent., though it varies considerably in different places. Fletcher (89) also reports carrier rates as high as 15 per cent. from the native schools of Kuala-Lumpa, but does not mention the virulence of these carrier strains of diphtheria bacilli; he does, however, mention that 90 per cent. of fifty cultures which were isolated from diphtheria patients were toxigenic. This author also remarks that the bulk of the morbidity from diphtheria in the Asiatics of the Federated Malay States falls on children below the age of five years, which is of interest as regards the Schick test graphs for Malays in Fig. 3, which included no children under 5. Gomez and Navarro (93) also state that the diphtheria carrier rate among 1,775 Fillipinos was 2·08 per cent., but of thirty-five cultures isolated only four were typically virulent, which gives a virulent carrier rate of only 0·3 per cent. Therefore it seems that although diphtheria bacillary carriers are just as common in many parts of the tropics as in the towns of higher latitudes, yet diphtheria is very scarce and Schick immunity very high. Doull (94), who has made a most valuable analysis of the morbidity statistics of some infectious diseases in relation to latitude, came to the conclusion that latent or subclinical infections are more common in southern than northern latitudes, and that the brunt of infection in the south falls on the very young. He notes that even a comparison of the Southern with the Northern United States shows that the percentage of total diphtheria incidence for the age group of under 5 years is 50 per cent. in Alabama, as against 21 per cent. in New York. He refuses to believe that this is due to the greater exposure of the younger children in the South, or otherwise the same increase of concentration of infection on the younger ages would appear with measles and whooping cough, which it does not. I do not think this argument is altogether valid; because studies in the spread of infection (95) have led me to believe the striking distance of the latter diseases are so much greater than that of *clinical* diphtheria, that a decrease in closeness of contact, which might have no appreciable effect on measles, might have a very significant one on the incidence of diphtheria. Native populations, even if sparsely distributed as regards square miles, often live in the closest of contact in crowded, cramped, unventilated huts and villages, where the younger children congregate; and the closeness of contact is often greater than that which is seen at the present day in the worst slums of any northern city. It is also to be noted that in these native habitations thousands of young children may sicken, or even die, without any white man having the faintest idea of what infections they suffered from. In regard to this point, Fletcher (89), in the report on diphtheria in the Malay States, definitely says 'Malays seldom bring their children to a hospital for treatment'. Therefore a high percentage of Schick

immunes in tropical latitudes could probably be accounted for, as it undoubtedly is elsewhere, by the type of environment, and to the probability that the natives of the tropics are exposed to an intense environmental stimulus during the earliest years of life. This would result in just such a Schick test and age graph as is shown for the Philippines in Fig. 3. Also, the absence of clinical diphtheria from the tropics may be more apparent than real; should it be true that the bulk of the incidence falls on the very young. Moreover, diphtheria in children under two is often atypical, and coloured patients of this age are rarely seen by a doctor. Should it be true that the infants experience an intense antigenic stimulation from the time of birth, it is not unreasonable to assume that many native infants acquire active immunity without symptoms before they even lose their maternal passive immunity. This hypothesis would explain an actual, as well as an apparent, diminution in the incidence of clinical diphtheria in low latitudes. The weather also is an important secondary factor that should not be lost sight of. Diphtheria in temperate zones is essentially a seasonal disease. In the tropics there are no seasons. It is possible that lack of a yearly periodic disturbance in the balance between host and parasite results in a closer mutual adaptation between them. This close adaptation would mean a high Schick immunity in combination with a high ratio of carriers to cases of diphtheria, such as is seen in the tropics. A very indirect but suggestive piece of evidence bearing on this point is given by Vardon (92). He has found the ratio of the virulent to the avirulent strain of diphtheria bacilli in India to be about 1 : 7. Also Gomez and Navarro's (93) figures, already referred to, show a ratio of 1 : 8 virulent to avirulent Fillipino carriers. In England this ratio averages about 1 : 2 but is extraordinarily variable at different times and places. If, as is now usually granted, the avirulent bacillus is often a descendant of the virulent variety of the same species, the great preponderance of the non-toxic variety may well be a good indication that in hot climates there is a closer adaptation between man and *C. diphtheriae.*

The question of a real racial immunity to diphtheria also requires consideration. No one of course supposes the dark races are born with an *active* antitoxic immunity, but they may be born with a greater and more rapid facility of responding to the diphtheria bacilli in the environment. This is a very difficult hypothesis to prove, and the only really suggestive observation on the point which I have been able to find is a statement, without any details, by Frost (75), who says that the negroes of Baltimore show the same carrier rates and Schick immunity as the white population living under similar conditions; but that the black attack rate for clinical diphtheria is only one-third that of the white. If the statistics on which this statement is based are significant, and Frost admits the observations 'are not extensive', a real racial immunity may be a factor in the causation of the high percentage of Schick negative reactors found in low latitudes.

Since the above section was written, Heinbecker and Irving-Jones (96) have published a unique study on the susceptibility of the Polar Eskimos to the

common cold, diphtheria, and scarlet fever. They made the curious discovery that although exhaustive inquiry could not elucidate the history of anything resembling a diphtheria epidemic, yet 37 out of 49 Eskimos of various ages were Schick immune. The authors were 'forced therefore to conclude the immunity shown does not depend on infection by the diphtheria bacillus'. These results were not due to bad toxin, because the authors of this obviously careful investigation brought samples of Eskimos' blood sera back with them and found that they contained about 0·1 unit per cc. of diphtheria antitoxin when titrated by Romer's method, and also that Eskimos' sera were capable of protecting guinea-pigs from lethal doses of diphtheria toxin. There is, however, one very significant fact about this small group of tests. *All* the children under twelve were Schick positive reactors, whereas *all* subjects, with one doubtful exception, over this age were immune reactors. This absolutely abrupt change over at a definite age from susceptible to immune seems, to my mind, more easy to attribute to an intense antigenic stimulus of short duration which took place twelve years previous to the Schick investigations, than to any hereditary phenomenon. That such an hypothesis is not outside the limits of likelihood is supported by the interesting observations given in the same paper on the habitual behaviour of the minor respiratory infections among the Polar Eskimos. Whenever any visitors, who themselves may seem in perfect health, from the outside world make contact with an Eskimo community, the whole population becomes infected within two or three days with respiratory colds and bronchitis. 'The infection subsides and does not reappear until another contact has been made with the outside world, no matter how long delayed.' Thus within the space of a few days there is a 100 per cent. incidence, then complete absence of illness until infection is reintroduced. If a mild diphtheria bacillus had been introduced to this Eskimo community and had behaved in the same way as other droplet-spread diseases, twelve years later, all the members of the community under 12 years old would have been expected to have positive Schick reactions, while the majority of those over twelve would have been expected to be immune : just as Heinbecker and Irving-Jones report. It should be mentioned that these authors also were unable to obtain a *single* positive Dick test among 50 Eskimos, or any history of clinical scarlatina. This is, if anything, a still more difficult observation to explain away than the high percentage of Schick immunes. However, toxigenic streptococci are ubiquitous in other parts of the world, and according to some authorities all streptococcic toxins are similar to that of scarlatina, which is a possible, if rather weak, way of escape from having to believe such specific substances as bacterial antitoxins appear of their own accord in the blood, as a physiological phenomenon having no connexion whatever with the homologous toxins. It is to be earnestly hoped that opportunities may occur in the future of pursuing this investigation on the immunity reactions' epidemiology, and more especially the normal commensal bacteria, of the Polar Eskimos, who at the present day must be the most isolated race in the world.

25. *The Genetic Factor in Schick Immunity.*

A word of introduction is necessary to explain what the heading of this section really means. Active antitoxic immunity to diphtheria is an acquired character, and as such is probably not inherited. (Congenital immunity is passive and does not effect the subject.) The potentiality to produce antitoxin is a property of the germ plasm of the human species, and of course is inherited. This genetic potentiality to make antitoxin, when circumstances require it, is part of the mechanism by which the human species becomes adjusted to its bacterial environment. The potentiality to produce antitoxin will be latent, unless stimulated by the appropriate antigen, which is either diphtheria bacilli, naturally present in the environment, or artificially administered diphtheria prophylactics. It has been practically proved by the numerous observations recorded in this essay, that the degree of Schick immunity, the rate of its production and susceptibility to diphtheria, depend on the quality, quantity, and spacing of the antigenic stimuli, which the hereditary mechanism for producing antitoxin has received throughout an individual's life. The question to be answered is: are the variations in antitoxic immunity, and the rate at which it is acquired, to be explained by variations, if any, in the quality of the hereditary germinal mechanism of different individuals and races of men, or by qualitative and quantitative variation in the environmental stimuli which act on a hereditary immunity mechanism, which is similar in all members of the human species? The supporters of the hypothesis, that susceptibility to diphtheria is chiefly a hereditary defect in the potentiality to produce antitoxin, point out that certain groups of children seem to resist all attempts to immunize them, and that the majority of individuals who pass through an attack of diphtheria remain Schick positive reactors. But, as was shown in sections 20 and 14, very few subjects prove altogether refractory to active immunization, and the fraction of slow antitoxin producers becomes progressively smaller the more experience the whole group has had of diphtheria bacilli. Moreover, those who have had diphtheria loose their Schick positive reactions quicker than normal when re-exposed to an antigenic stimulus, all of which seems to imply that lack of previous experience of bacteria, rather than a genetic defect in the immunity mechanism, is the chief reason for the observed resistance to prophylactic injections shown by certain subjects, and their susceptibility to clinical infection. The seeming immunity of coloured races to diphtheria, and Frost's observation on the differential morbidity between the negroes and the white races in Baltimore, are suggestive of a real racial difference in susceptibility to diphtheria. In this connexion Hirschfeld's (97, 98) observations are of great interest. By blood grouping and Schick testing the same individuals by families, he found that the potentiality to form antitoxin seemed to be inherited with the blood group. If the parents had different Schick reactions, and also belonged to different blood groups, the children whose blood group was the same as that of the parent with the positive Schick reaction were also positive. The same did

not apply with regard to negative reactors. This observation is evidence that the genetic factor in Schick immunity does vary considerably, especially when it is considered in conjunction with the following deduction. In a population where diphtheria is endemic the decline in susceptibility seems to descend to a certain level and then cease. In the poorer districts of large European and North American cities this stabilized level of the herd immunity seems to occur at about 15 per cent. of Schick positive reactors, and takes about 20 years to reach. That is, the 20-year-old inhabitants show the same degree of herd immunity as all the older age groups. This phenomenon is well shown in the Philippine curve, Fig. 3. Here the curve declines rapidly, and in this case reaches its minimum in ten years, instead of 20, and the level at which the curve becomes horizontal, which indicates that the herd immunity is now constant, is 6 per cent., instead of 15 per cent., as seen in Europe. I think Gomez's figures are significant because the age group samples between 10 and 18 numbered 515, and over 18, 381, and the percentage positive in these two groups were 5 and 6 respectively. If this cessation of the decline in herd susceptibility at a definite level is a real phenomenon, it means that there must be a group of individuals who will not respond to the antigenic stimuli of the average intensity peculiar to their environment for however long the stimuli continue to act. Therefore such individuals must have less power than normal of producing diphtheria antitoxin. They suffer from a genetic defect in their adaptation mechanisms, and are therefore biologically less plastic than the rest of their herd. It must be carefully noted that it is the refusal of the susceptibility curve to sink below a definite level once a certain age group has been reached that is of significance. The magnitude of the co-ordinates, representing age and Schick susceptibility, which determine this point does not matter. Again, the fact, that when the Philippine curve is contrasted with European curves the decline is more rapid and proceeds to a lower level in the former than the latter, is just as strong evidence that these phenomena are due to differences in the intensity of the natural antigenic stimuli in Europe and the Philippine Islands, and is not of necessity due to any genetic variation in the constitution of the two races.

If this hypothesis is true, then most adults, who have Schick-positive reactions in environments where diphtheria has been prevalent, are those who are resistant to those environmental antigenic stimuli which were sufficient to render immune most of the fellow members of their herd. If Hirschfeld's observations are now reconsidered, in conjunction with the above hypothesis, it becomes evident that a parent who has a Schick positive reaction will usually belong to this group of individuals who are bad antitoxin producers. Therefore, if the potentiality for acquiring antitoxin is linked with that of producing haemagglutinins, the child who belongs to the same blood group as the Schick positive parent will remain a Schick positive reactor in the face of the same environmental stimulus, whose intensity was too weak to immunize the parent. On the other hand, if the child's blood group is the same as that of the parent with a negative Schick reaction, it will be a positive or negative reactor,

according to its age and diphtherial experience, which accounts for the observed correlation between negative Schick reactors and their children of the same blood group, and the agreement, when in such cases the Schick reaction of the parent is positive. The Hirschfelds' (99) earlier investigations have demonstrated that the frequency distribution of the four human blood groups varies characteristically in the different races of mankind. In the inhabitants of the tropics Group III (Moss) predominates over Group II, while among Europeans the reverse is the case. Some incomplete work at Greenwich has so far failed to show any significant difference in the frequency distribution of the blood groups among (1) negative and positive Schick reactors, (2) boys who have, and boys who have not, a history of diphtheria, (3) boys who took a long time to become immune, and those who only required one dose of prophylactic. Hirschfeld, however, does not claim that the potentiality to form diphtheria antitoxin is linked to any special blood group, but even so, the evidence that haemo-agglutination and antitoxin-forming characters are inherited together makes the fact, that Schick immunity and haemo-agglutination also vary in different parts of the world, suggestive of a genetic racial variation in susceptibility to diphtheria. The evidence for a difference in sex susceptibility to diphtheria was discussed in section 23, and was undoubtedly strongly in favour of the view that the potentiality to form antitoxin was more highly developed in the male, such a difference if proved would be genetic in character. Lastly there is the phenomenon known as 'Zingher's law', which is usually brought forward as evidence of the hereditary factor in Schick immunity. Zingher, Park, and Serota (100) were the first authors who noted that, in general, all the members of a family have the same Schick reaction, and when there are both positive and negative reactors present, it is the youngest members of the family who are Schick susceptible. Many observers have confirmed 'Zingher's law' as a rough general rule with many exceptions. For instance, Dickenson (10) found that the members of 71 per cent. of 84 families were either all immune, or all positive, reactors. He does not remark what agreement he found with the second part of the 'law'. 'Zingher's law', especially as the exceptions are relatively numerous, is exactly what would be expected on the hypothesis of natural and latent immunization. If a family has had no experience of diphtheria, all its members will naturally be Schick susceptible. If diphtheria bacilli are now introduced, the closeness of family contact will generally ensure that each member either becomes latently immune or gets diphtheria. The other part of the law is also what is to be expected, the older members will tend to become immune before the younger, because they will have had more chances of being immunized either in or outside the family, or the younger members will remain Schick positive since they may well have been born after the diphtheria bacillus had visited the family and departed again; in a similar way to those boys who joined Greenwich School after an epidemic had come and gone, and therefore remained with the same degree of immunity until the next diphtheria epidemic matured. 'Zingher's law', to my mind, is better explained by the acquired immunity, rather than by

the hereditary immunity hypothesis. In fact it was only by examining the exceptions to Zingher's law that Hirschfeld was able to put forward the best evidence so far produced in favour of a variable genetic factor in antitoxic immunity to diphtheria. A general survey of the evidence does undoubtedly suggest that a small percentage of the population are born with genetic defects in their potentiality to form diphtheria antitoxin, but that this hereditary factor has an insignificant bearing on the degree of immunity possessed by a community as a whole, compared with the concentration, distribution, and persistence, of diphtheria bacilli in the environment. In other words, it is probable that individuals do vary to a considerable degree in their hereditary faculties for the production of diphtheria antitoxin; but the frequency distribution of such individuals, of different degrees of genetic susceptibility, must be so regular throughout the community, and perchance throughout the whole world, that the genetic factor has little influence in determining the statistical variations in Schick immunity, diphtheria morbidity, and fatality, seen at different times and places.

26. *Schick's Reaction and the Advance of Medical Science.*

Diphtheria, even before the advent of the Schick test, was undoubtedly a good subject to select for studying the relationship between men and microbes; because both clinically and bacteriologically diphtheria is a very definite entity. The diphtheria bacillus produces a toxin of very constant properties which in turn stimulates the formation of an equally characteristic antitoxin about whose therapeutic value, even the most sceptically minded of reliable observers have no doubt. When a simple and trustworthy immunity test was added to these other attributes, the possibility of unravelling some of the complexities in host-parasite relationships became far greater in diphtheria than in any other infectious disease. It at once became possible to test, directly on the human subject, the efficiency of prophylactic agents and of the technique employed in their administration, and to separate the host factor from the parasite factor in the study of infection with the diphtheria bacillus. By means of the Schick test, combined with other methods, a large amount of knowledge has been accumulated regarding diphtheria and its epidemiology. The demonstration, which has been given by the Schick reaction and diphtheria of what a powerful instrument a simple immunity test can be in elucidating the natural history of a disease and bringing it under control, has encouraged research along the same lines in other diseases. By taking diphtheria and the Schick test as a model, practically all the main conclusions, on the herd immunity and epidemiology of diphtheria have been proved to hold good for scarlet fever, by means of the Dick test. For instance, Debré and Lany (101) were able to declare that latent immunization occurs in scarlet fever. In one institution just after an outbreak of scarlatina only 18 per cent. of the children had positive Dick reactions, while in similar institutions where there had been no epidemic 36 per

cent. were Dick susceptible. Harries (27) also gives many tables of parallel Schick and Dick statistics which demonstrate that the dissemination mechanisms of scarlet fever infection, and production of immunity against it, must be very similar in both diseases. Again, largely owing to the stimulus produced by the success of Schick's reaction, there has been a great revival of research on the effect of bacteria and their products on the human skin in hope of finding simple diagnostic and immunity tests for other diseases. As examples of this type of work, Herrold and Trant (102), using a filtrate of a culture of pneumococci found that whereas only 25 per cent. of pneumonia cases reacted to it on interdermic injection, 80 per cent. of normal controls responded to this filtrate. Fleisher and Tierney (103), employing filtrates from cultures of *B. typhosus*, got no reactions in typhoid fever cases, but positive reactions in controls, while Glukoff (104) produced a typhoid 'endotoxin' which gave a reaction with patients, but not with normal people. A reliable typhoid immunity test would be of inestimable value to the services in the control of anti-typhoid inoculations. At present it is unknown what proportion of, and to what extent, men who are inoculated with enteric vaccines are protected against infection with enteric bacilli. The outlook is hopeful for the future, but at present most of the newer work on skin immunity reactions is only in the experimental stage, and the results are often hard to co-ordinate. Dold, in a series of admirable reports (105), has been systematically investigating the skin reactions of guinea-pigs and rabbits to all kinds of bacteria, and has produced a mass of valuable observations, which should prove of great practical assistance to all who are working on human skin reactions. It is worth noting that some of these new skin reactions are analogous to the Schick reaction proper, where a poisonous substance irritates the skin unless the subject possess an antidote to it, but many more seem to be allergic phenomena indicating a present, or recent, infection with the organism from which the injected reagent was produced. Such allergic reactions are therefore more analogous to the pseudo-Schick, or diphtheria-protein, reaction. It is therefore desirable that every advantage should be taken of using the quantity of material, at present available in anti-diphtheria work, for studying the diphtheria protein reaction in hope of finding clues that may ultimately be useful in pointing the way to the discovery of practical immunity tests for other infections. But to my mind the most important advance in scientific medicine, which is almost entirely due to the Schick reaction, is that for the first time we possess a reliable instrument for separating the host and parasite factors in the spread of disease. For example, before the advent of the Schick test, it had frequently been noted that diphtheria epidemics in country districts were often more severe and extensive than in towns. It was impossible to say whether this phenomenon was caused by some factor in the rural environment causing an increase of parasitic virulence, or to a difference in the resistance of the inhabitants of the country and the town. On the whole, considering the better physique and healthier lives of countrymen, compared with town dwellers, the first hypothesis would have seemed the more logical; but since the Schick

test has shown that the percentage of immunes in the city is often four times as great as in the country, it becomes tolerably certain that it is the known susceptibility of the country men to diphtheria, rather than an imaginary alteration in the virulence of the bacillus, that is the more important factor in determining the difference in the characters of rural and urban diphtheria epidemics. The combined study of the spread and distribution of diphtheria bacilli and Schick immunity has clarified our concepts of diseases of the herd, (i. e. endemics and epidemics), to extent that is as yet scarcely realized. The application of the lessons, which the Schick test has taught about the spread of diphtheria, to the analysis and comparison of morbidity statistics collected at different times and places is already beginning to throw light on some of the difficult problems of epidemiology. For all these reasons medical men, even if their daily tasks do not bring them into contact with diphtheria, and the laboratory is not their normal environment, should remember the names of Römer and Schick.

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AN INVESTIGATION OF BLOOD-PRESSURE, PULSE-RATE, AND THE RESPONSE TO EXERCISE DURING NORMAL PREGNANCY, AND SOME OBSERVATIONS AFTER CONFINEMENT[1]

By D. C. HARE and M. NOEL KARN

The object of this investigation has been to study by clinical methods the physiological reactions of the circulation during the course of normal pregnancy. The methods employed were blood-pressure and pulse-rate measurements and the response of the pulse-rate to an exercise test. The greater number of observations, about three-fourths of the total, have been made on individuals who were examined several times at intervals of four weeks or more; other records are from patients who were seen only once. The figures obtained have been examined statistically; as a rule for statistical purposes a large number of records taken from unselected individuals form the best sample, in pregnancy, however, at any given time the distinction between normal and pathological variations may be difficult. The method of repeated examination of the same patients has the advantage that the patients can be easily followed up and those who prove to be definitely abnormal excluded, emotional reactions become minimized by familiarity, and the co-operation of the patients is obtained so that they submit readily to tests even in the later months.

The report on conditions in pregnancy is based on the examination of 106 individuals who made 468 attendances and on 145 individuals seen once or twice only. Of this total 121 were primiparae and 130 multiparae. The patients were drawn from the wards and ante-natal clinic of the Obstetrical and Gynaecological Unit of the Royal Free Hospital by kind permission of Professor McIlroy. A more limited study of women up to six months after confinement has also been made, based on 203 records.

Circulatory tests, such as those used here, have been applied to large groups of persons by various workers, and classifications of physical efficiency have been elaborated from them. These were widely employed during the war; a summary of these methods, and the results of the application of certain physical efficiency tests to groups of women, was published by the Medical Research Council in a report by Lucy D. Cripps (1); this is of special value, as little work of this kind has been done on women in England. A valuable study of blood-pressure and pulse-rates in early life has been published by P. Stocks (2); to both these reports frequent reference is made in this paper. No detailed studies of the

[1] Received November 21, 1928.

circulatory changes in normal pregnancy appear in recent literature, and the value of older reports suffers from the unreliability and variety of the methods employed. In 1908 Slemons and Goldsborough (3) reported on a study of 10 cases examined repeatedly, but the data used appear to be insufficient; and in an article by Vaux (4) on blood-pressure in pregnancy no statement is made of the number of observations or methods on which the general conclusions are based.

Methods of Selection and Tests Employed.

The importance of using methods which are comparable with those of other workers has been kept in view.

Examination of the heart was made in all pregnant cases, and where the history or findings suggested abnormality the patient was watched, examined if necessary by electrocardiograph, and finally excluded if abnormal. Cases of irregularity due to extra-systoles were not excluded unless this was considered to be associated with myocardial disease, but occasionally the irregularity was so persistent as to make the accurate record of blood-pressure and pulse-rate difficult. All the pregnant women were seen at each attendance in the ante-natal department, and their general condition was under the supervision of both the obstetrician and chemical pathologist in that department. Evidences of toxaemia were thus detected early.

The period of pregnancy has been calculated when possible from the actual date of confinement, correction being made for a statement of prematurity of the infant. Where the patient could not be followed up, the woman's own dates were used for the calculation, checked by the report of the doctor in the ante-natal department.

The conditions of the examination were uniform as far as possible, and with the pregnant patients the routine could be closely followed. The patients were seen in the morning between 10 and 12 noon. On arrival they were put to rest on a couch for a full twenty minutes before any records were made. The couch raised the head and shoulders, and this was varied to suit the comfort of the patient. The average lifting of the head was twelve inches, and this is described as the 'lying' position. After the rest the pulse-rate was counted for a full minute and the blood-pressure taken. A mercury manometer and a soft 12 cm. cuff were employed, and care was taken that the arm was supported, the muscles relaxed and the elbow slightly flexed. Each reading was made as quickly as possible, and long compression producing congestion of the arm avoided. With the first compression a reading of the radial pulse was made, the results not being used for record but serving to check the auscultation readings. Right and left arm readings were made simultaneously by two observers, tubes being led from the pressure bands to the same manometer. The two workers were able to compare and check their results; this was useful in the case of difficult readings and also served to keep uniform standards, an important point when making readings by auscultation. The systolic reading was made at the first point (i. e.

the sudden appearance of a clear tapping sound), the diastolic reading was made at the fourth point (i. e. the end of the third phase), and when this was absent the reading was made at the point of cessation of the sound, it being assumed that the fourth point is coincident with the fifth in such cases (Stocks). Individual cases were found in whom the auscultatory readings were difficult owing to the faintness of the sounds. This was rarely so with the systolic, but more frequently with the diastolic; opening and closing the hand vigorously a dozen times often made it possible to take a satisfactory reading. Right and left arm readings were recorded in all cases. The left arm readings only are used in the general discussion and tables in accordance with the recommendation of Stocks.

After sitting for five minutes in an upright chair, pulse-rate and blood-pressure records were taken in the same way as when lying; the standing pulse-rate was recorded for two consecutive minutes, in four half-minute periods. An exercise test was given as described on page 392 below. The weight was noted at each attendance and the height recorded.

Examination of Control Cases.

It was thought advisable to obtain observations on non-pregnant women by precisely similar methods, and as it is probable that social class and occupation have a considerable influence on the blood-pressure, three groups of controls were tested. The medical history was taken and doubtful cases rejected, but no examination of the heart was made. The results are given for comparison with those of the pregnant women in the text and tables. The groups tested were (1) 'Welfare Mothers.' Working-class mothers six months or more after a previous confinement and not again pregnant. Examinations were made in the afternoon, and included pulse-rates and blood-pressures only. (2) Laundry women between the ages of 20 and 45 from the staff of a large laundry. The women were examined on the laundry premises during the morning hours, and came direct from their work. The employees of this firm had been the subject of previous investigations and co-operated very readily. After ten minutes rest they were given the pulse-rate, blood-pressure, and exercise tests. (3) Women medical students. Tests were carried out as with the last group. They were examined during the morning, and came direct from class work.

Blood-pressure Observations.

The mean systolic pressure of the pregnant women is low throughout the whole period of pregnancy, when compared with the figures for normal control groups. There is possibly a tendency to lower pressures in the middle period than in the early weeks, and a slight rise is found in the last weeks. Examination was made in both the sitting and lying positions, and the difference between the means of the readings in the two positions is insignificant when examined mathematically.

Systolic Pressure—Pregnant Cases.

Weeks.	Obs.	Sitting Sys. Pr.	Obs.	Lying Sys. Pr.	Increase or Decrease on Sitting Pr.	Mean Age.
5–20	67	113·41 ± 0·72	88	113·37 ± 0·68	−0·04	
21–	54	112·16 ± 0·80	72	113·27 ± 0·75	+1·11	
25–	91	111·93 ± 0·62	104	112·96 ± 0·62	+1·03	
29–	102	114·83 ± 0·58	104	112·88 ± 0·62	−1·95	
33–	103	114·60 ± 0·58	108	112·57 ± 0·61	−2·03	
37–	107	116·02 ± 0·57	106	114·63 ± 0·75	−2·39	
All Weeks.	524	114·07 ± 0·26	582	113·28 ± 0·19	0·79 ± 0·32	28·09
		s. d. 8·72		s. d. 9·43		s. d. 5·98

See Curve I, p. 387.

Female Controls.

	Obs.	Sitting Sys. Pr.	Standard Deviation.	Mean Age.
Welfare mothers	113	120·10 ± 0·65	10·24	29·58
Laundry workers	49	123·74 ± 1·25	12·96	28·36
Students	50	119·38 ± 1·06	11·21	21·90
Students (Stocks)	98	121·70 ± 0·72	—	20 to 35
Students (Cripps)	115	125·62 ± 0·75	11·98	21·13
Clerks (Cripps)	125	123·54 ± 0·62	10·30	26·34

Weeks = Weeks of pregnancy. Obs. = Number of observations.
Sys. Pr. = Systolic pressure. s. d. = Standard deviation.

The mean diastolic pressure for the whole period of pregnancy is not significantly lower than that of the controls who form the most strictly comparable group, but for the first six months the mean pressure is below the general mean and during the last three months above it, reaching the maximum in the ninth month. The differences between the means of the records in the sitting and lying positions are insignificant.

Diastolic Pressure—Pregnant Cases.

Weeks.	Obs.	Sitting Diast. Pr.	Obs.	Lying Diast. Pr.	Increase or Decrease on Sitting Pr.
5–20	63	70·77 ± 0·69	88	70·40 ± 0·61	−0·37
21–	52	69·57 ± 0·76	72	70·22 ± 0·67	+0·65
25–	92	70·32 ± 0·57	104	70·76 ± 0·56	+0·44
29–	101	73·93 ± 0·55	103	72·17 ± 0·56	−1·76
33–	100	75·66 ± 0·55	105	75·25 ± 0·56	−0·41
37–	105	78·94 ± 0·54	105	78·75 ± 0·56	−0·19
All weeks	513	73·82 ± 0·24	577	73·16 ± 0·24	
		s. d. 8·18		s. d. 8.45	

See Curve II, p. 387.

Female Controls.

	Obs.	Sitting Diast. Pr.	Standard Deviation.
Welfare mothers	113	74·74 ± 0·51	8·01
Laundry workers	49	78·54 ± 0·70	7·28
Students	50	77·81 ± 0·62	6·52
Students (Stocks)	98	81·80 ± 0·55	—
Students (Cripps)	115	75·10 ± 0·62	9·83
Clerks (Cripps)	125	75·25 ± 0·55	9·09

Correlation of the number of weeks of pregnancy with the diastolic pressure gives a definitely significant positive coefficient, viz. : $r = 0{\cdot}357 \pm 0{\cdot}026$.

The pulse-pressure is the difference between the systolic and diastolic pressures, and not itself a direct measurement. The mean pulse-pressure for the whole period of pregnancy is on the low side of the normal range. The figures for the earlier months are within the normal range, but there is a steady fall, and in the last period, the 37th to 40th weeks, the lowest mean figure is obtained, which is approximately 8 mm. below the mean for the 'Welfare Mothers'. The figures for the control cases show considerable variation.

Pulse-pressure—Pregnant Cases.

Weeks.	Sitting.				Lying.			
	Obs.	Sys. Pr.	Diast. Pr.	Pulse Pr.	Obs.	Sys. Pr.	Diast. Pr.	Pulse Pr.
5–20	63	113·41	70·77	42·64	88	113·37	70·40	42·97
21–	52	112·16	69·57	42·59	72	113·27	70·22	43·05
25–	91	111·93	70·32	41·61	104	112·96	70·76	42·20
29–	101	114·83	73·93	40·90	103	112·88	72·17	40·71
33–	100	114·60	75·66	38·94	105	112·57	75·25	37·32
37–	105	116·02	78·94	37·08	105	114·63	78·75	35·88

	Sitting Pulse Pr.	Standard Deviation.
Pregnant Cases (all weeks)	40·10 ± 0·25	8·30
Female Controls.		
Welfare mothers	45·31 ± 0·58	9·16
Laundry workers	45·72 ± 1·05	10·85
Students	41·34 ± 1·02	10·77
Students (Stocks)	39·90 ± 0·67	
Students (Cripps)	50·52	
Clerks (Cripps)	48·29	

Correlation of the pulse-pressure with the number of weeks of pregnancy gives definitely significant negative coefficients, viz.:

Sitting pulse-pressure and duration of pregnancy, $r = -0{\cdot}256 \pm 0{\cdot}028$.

Lying " " " " $r = -0{\cdot}274 \pm 0{\cdot}026$.

The fall in the pulse-pressure is related to the progressive rise of diastolic pressure associated with the much slighter rise of systolic pressure.

Blood-pressure in relation to age in pregnant women. It is now generally agreed that there is no increase of blood-pressure with age in healthy adult individuals, men or women, up to the age of 40 years. An examination of the systolic pressure in relation to age has been made in the present investigation, and is set out in the table blow. The differences between the age groups taken as a whole are negligible, though the age group over 35 years shows an increase of 1·76 mm. Hg. systolic pressure above the general mean.

Pregnant Cases.

Age.	Obs.	Sys. Pr. (Sitting).
Up to 24	177	114·05 ± 0·44
25 to 29	182	114·47 ± 0·44
30 to 34	94	112·01 ± 0·61
35 to —	71	115·84 ± 0·70

The coefficient of correlation between age and systolic pressure (sitting) is $r = 0{\cdot}015 \pm 0{\cdot}030$.

Blood-pressure in relation to posture, and to period of pregnancy. The effect of the sitting and lying positions on systolic pressure has been studied. The sitting pressure shows a slight increase over the lying pressure, but this is less than 1 mm. Hg. on the mean of all observations, and the actual reading may be above or below. These results are in accordance with those of other workers (Wheelon (5)). When considered in relation to the month of pregnancy it is seen that there is a tendency for the sitting pressure to increase over the lying pressure in the last three months, reaching a maximum increase in the last month of 2·39 mm. Hg.

Combining the observations from the 21st to the 28th weeks, the mean pressure in the sitting position is $112{\cdot}02 \pm 0{\cdot}49$, which is significantly less than the mean reading at the 37th to 40th weeks, the difference being $4{\cdot}00 \pm 0{\cdot}75$.

The correlation of the number of weeks of pregnancy with the systolic pressure (sitting) is $0{\cdot}125 \pm 0{\cdot}029$, which is just significantly positive; and with the systolic pressure (lying), it is $0{\cdot}020 \pm 0{\cdot}028$ which is insignificant.

Standing pressures have not been taken in these observations, nor lying pressures in the series of control cases.

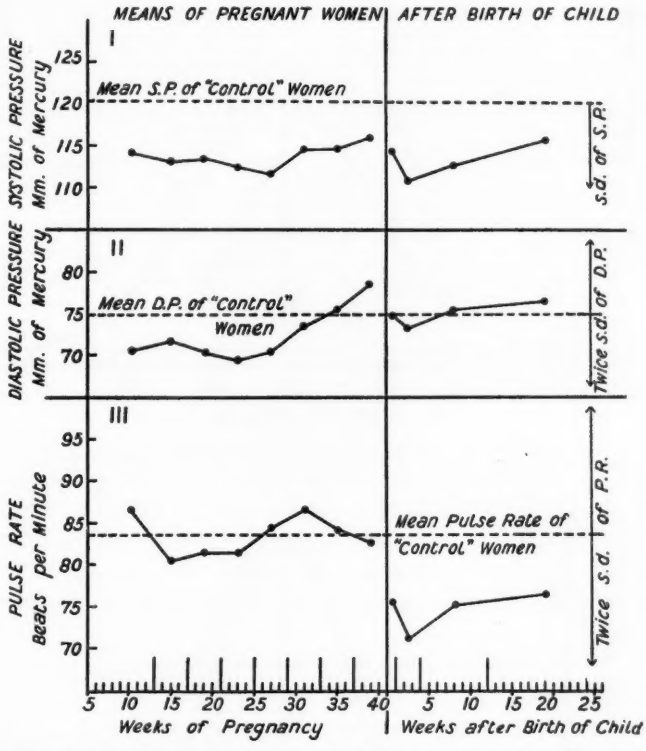
Blood-pressure in relation to weight. A definite though small positive correlation has been shown to exist between systolic pressure and weight in normal individuals, but for diastolic pressure the correlation with weight is insignificant. In pregnancy the examination of this factor presents difficulties. The weight is steadily increasing as the foetus develops, but the rate of increase probably depends to some extent upon the normal weight of the mother, which is not known; further, it cannot be assumed that an increase of weight due to foetal development will produce physiological reactions directly comparable with those of normal individuals. The correlation of weight and systolic pressure is given for the pregnant cases and controls. The weights being taken in ordinary indoor clothing are approximate only, and the pregnant patients were usually weighed in the same clothes at each attendance.

	Mean Weight.	Mean Sys. Pr.	Correlation Co-efficient.
Pregnant cases (Average duration of pregnancy 28·5 weeks)	61·06	114·07	$r = 0{\cdot}247 \pm 0{\cdot}029$
Welfare mothers	58·03	120·10	$r = 0{\cdot}272 \pm 0{\cdot}060$
Laundry workers	56·23	123·74	$r = 0{\cdot}216 \pm 0{\cdot}091$

Blood-pressure in relation to height. It has been shown that for normal adult males (Stocks (2), Huber (6)) the relation of systolic pressure and height is negligible, while the diastolic pressure and height shows a very slight degree of positive correlation. No figures are available for normal women, and the correlation has therefore been omitted in the present study.

The range of blood-pressures in normal women. The diagrams show the distributions in normal curves of the systolic and diastolic pressures of the 'Welfare mothers' and pregnant women.

The normal distribution of systolic pressure of 'Welfare Mothers'. The tables of the probability integral show that positive and negative deviations from the mean as great as 25·0 mm. may each be expected to occur once in 100 cases. This means that in 100 cases, one case may be 97 or lower, and one case may be 147 or higher. The majority, 86 per cent., will lie between the limits 106 and 138 mm.



The short verticals indicate single weeks. The long verticals indicate the number of weeks included in the calculation of each mean.

S.P. = Systolic Pressure. D.P. = Diastolic Pressure. P.R. = Pulse-rate.
s. d. = Standard Deviation of Mean.

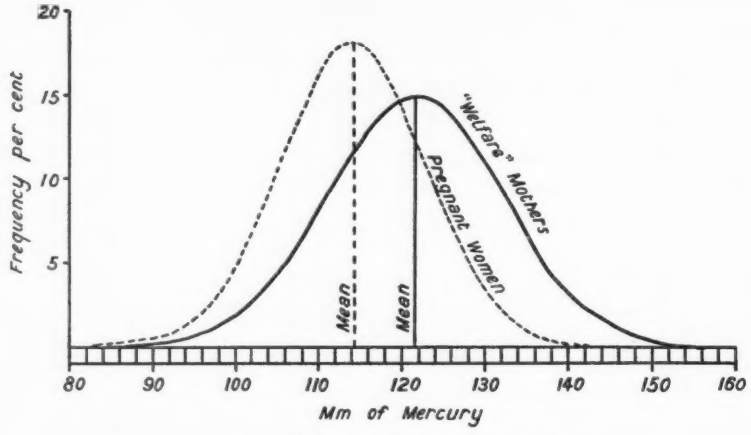
CURVES I–III. Curves of Systolic and Diastolic Pressures and Pulse-rate.

The normal distribution of systolic pressure of pregnant women. Positive and negative deviations from the mean as great as 20·3 mm. may each be expected to occur once in 100 cases. It follows that in 100 cases, one case may be 94 or lower, and one case may be 134 or higher, while the majority of cases, 83 per cent., will lie between the limits 102 and 126 mm.

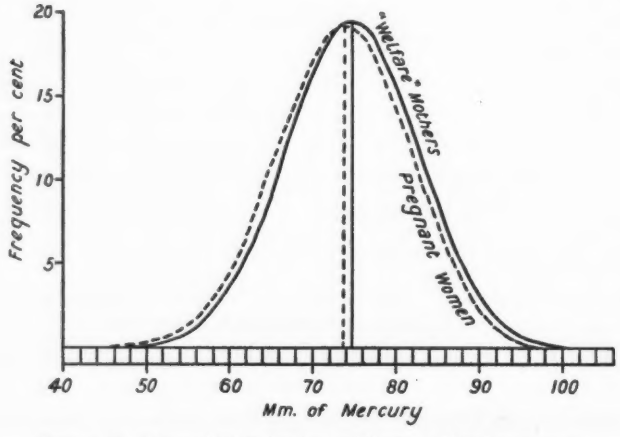
The normal distribution of diastolic pressure of 'Welfare Mothers'. Positive and negative deviations from the mean as great as 18·7 mm. may each be expected to occur once in 100 cases. It follows that in 100 cases, one case may be

56 or lower, and one case may be 93 or higher, while the majority, 92 per cent., will lie between 60 and 88 mm.

The normal distribution of diastolic pressure of pregnant women. The results are nearly the same as in the case of diastolic pressure of 'Welfare mothers'. In 100 cases, one case may be 55 or lower, and one case may be 93 or higher, while the majority, 91 per cent., will lie between 60 and 88 mm.



CURVE IV. Normal Distribution of Systolic Blood-pressures.



CURVE V. Normal Distribution of Diastolic Blood-pressures.

The tables below give, for certain groups of pressure, a comparison between the observed frequencies, and those calculated on the basis of a normal distribution.

In the distributions of systolic pressure, a tendency to somewhat larger frequencies of the high values than those given by the normal curve is indicated.

	Welfare Women.			Pregnant Woman.	
S. P.	Frequencies.		S. P.	Frequencies.	
mm. of Hg.	Observed.	Calculated.	mm. of Hg.	Observed.	Calculated.
Under 94	—	1	Under 90	—	1
*94– 98	—	2	90– 94	3	4
98–102	4	4	94– 98	9	10
102–106	8	9	98–102	21	24
106–138	213	214	102–126	435	436
138–142	11	10	126–130	38	30
142–146	6	5	130–134	8	13
146–150	4	2	134–138	5	5
150 and over	2	1	138 and over	5	2
	†248	248		524	524

* The pressure being read to a unit, this group includes values 93·5 to 97·5; and similarly for the other groups.

† In this distribution, every individual reading is included, instead of the average of three readings.

D. P.	Frequencies.		D. P.	Frequencies.	
mm. of Hg.	Observed.	Calculated.	mm. of Hg.	Observed.	Calculated.
Under 56	1	1	Under 56	3	7
56–60	3	2	56–60	16	14
60–88	104	104	60–88	465	468
88–92	3	4	88–92	17	16
92 and over	2	2	92 and over	12	8
	113	113		513	513

See Curves IV and V.

Records of cases with blood-pressures at the extremities of the range have been examined. Details of four patients with exceptionally low pressures, but otherwise apparently normal throughout pregnancy, are given below; a fifth case, No. 17, is included who, though not 'normal' in the earlier months, apparently became so in the later period without any concomitant changes in the blood-pressures.

Case No.	Age.	Pregnancy No.	Visits No.	Blood-pressures, range of means.			Remarks.
				Sys. Pr.	Dias. Pr.	Pulse Pr.	
46	26	1	4	93–101	67–79	20–32	Very well. Sick occasionally
48	31	1	3	95–101	55–69	28–46	Well throughout
106	27	3	6	96–105	61–77	24–35	Occasional vomiting, slight indigestion, otherwise well
114	32	2	3	96–101	53–71	33–43	Very well
17	29	2	6	90–95	63–76	22–30	See below
	After confinement			96–98	58–70	26–32	

No. 17 suffered from vomiting several times daily and occasional fainting attacks in the earlier months, but continued her usual life; on two occasions she fainted while lying on her back when under observation at the clinic; she stated that she never voluntarily assumed the dorsal position.

In the later months she felt very well and went out daily to work, but no rise of systolic pressure was found; seven weeks after confinement she was suckling and said she was 'very well', but the pressures were practically unchanged.

Records of two patients with exceptionally high pressures are given below, in whom no abnormality was discovered.

Case No.	Age.	Pregnancy No.	Visits No.	Blood-pressures, range of means. Sys. Pr.	Dias. Pr.	Pulse Pr.	Remarks.
68	20	1	2	130–155	72–83	53–78	Very well, occasional nausea
	After confinement			129	89–98	31–40	
61	19	1	5	121–139	75–92	40–51	Very well

Variations of blood-pressure. The differences between simultaneous readings in the right and left arm have been examined from the data available. It is found that the mean systolic pressure is higher in the right brachial artery than in the left.

Systolic pressure—Right arm $115{\cdot}74 \pm 0{\cdot}38$ standard deviation 8·61
Left arm $114{\cdot}07 \pm 0{\cdot}26$ „ „ 8·72
Difference $1{\cdot}67 \pm 0{\cdot}46$

This difference is found on examination to be a definitely significant figure, but the mean diastolic pressures are not significantly different; the higher systolic pressure in the right arm may probably be attributed to the greater average development.

The following are extreme examples of differences noted in pregnant patients between simultaneous readings in the right and left brachial arteries:—

Systolic Readings.

Case 53. Aged 25

	Lying Position.		Sitting Position. (Records taken 30 min. later.)	
	Right.	Left.	Right.	Left.
1st reading	142	127	136	135
2nd „	142	125	136	135
3rd „	139	133	135	135
Mean reading	141	128·3	135·7	135
Difference of means of right and left arms	12·7		0·7	

Observations on this patient on subsequent dates showed no marked differences between the right and left arm readings.

The following is an example of the persistence of the difference:—

Systolic Readings.

	Date.	Right.	Left.	Difference.
Case 37. Aged 30	14.10.24	124	118	6
		124	118	6
		133	123	10
Mean		127	119·7	7·3
Mean readings on subsequent dates	11.11.24	128	117	11
	9.12.24	120	114	6
	13. 1.25	130	115	15

Fluctuations of both systolic and diastolic pressure of several mm. Hg. have been frequently observed in the course of consecutive readings within a few

minutes. The systolic pressure is usually the more unstable. The high range of variation which may occur in the individual under constant conditions was first pointed out by Lewis (7), who ascribed them to variations in the amplitude of the heart-beat. Sewall (8) has more recently described waves of a slow rhythm and of an amplitude of even 25 to 30 mm. due to vasomotor variations which may occur at intervals of a few seconds to many minutes.

The records of forty cases of this series have been examined for successive fluctuations of systolic and diastolic pressure of 5 mm. or over. The number of visits paid was 197, the average per patient being 4·9 visits. The usual series of three readings taken on the left arm within two or three minutes gave two successive differences or chances of fluctuation. In regard to systolic pressure in 626 successive differences there were 99, or 15·8 per cent., which were as much as 5 mm. or more, and there were only two cases of a difference of 15 mm. or more. In diastolic pressure in the same number of chances there were 153, or 24·4 per cent., in which the difference was 5 mm. or more, and only one case of a difference of 15 mm. or more.

The possibility of the occurrence of such fluctuations should be remembered when taking pressure readings in clinical work ; a series of two or three readings to ascertain the range of pressure will give greater accuracy than single observations. The results of treatment directed to permanent alteration of blood-pressure levels should be accepted with reserve unless due allowance has been made for this factor of normal variability.

Pulse-rate Observations.

The mean rate of the pregnant women is approximately 84 per minute ; there are only slight changes in the mean during pregnancy, and the highest rate occurs in the 29th to 32nd weeks. The mean pulse-rate is approximately the same in the lying and sitting positions, being if anything slightly higher for the former. No observations in the lying position were made in the control series.

Pulse-rate at Rest.

Pregnant Cases.

Weeks.	Obs.	Sitting Pulse-rate.
5–20	61	82·20 ± 0·89
21–	50	81·30 ± 0·99
25–	90	84·72 ± 0·74
29–	95	86·86 ± 0·72
33–	102	84·07 ± 0·69
37–	103	82·91 ± 0·69

All Weeks.	Obs.	Sitting Pulse-rate.	Standard Deviation.	Obs.	Lying Pulse-rate.	Standard Deviation.
Pregnants.	501	83·97 ± 0·31	10·35	598	84·53 ± 0·29	10·64
Female Controls.						
Welfare mothers	125	83·60 ± 0·92	15·27			
Laundry workers	49	84·02 ± 0·90	9·42			
Students	50	82·30 ± 1·14	12·07			
Students (Stocks)	98	79·8				
Students (Cripps)	115	76·28 ± 0·64	10·16			
Clerks (Cripps)	125	73·82 ± 0·57	9·49			

See Curve III, p. 387.

The correlation between the number of weeks of pregnancy and the pulse-rate is $r = +0{\cdot}041 \pm 0{\cdot}030$, but this figure is not of value as it may be seen from the table above that the regression is not linear.

The correlation between the weight and pulse-rate has been shown to be of no significance in normal persons (Stocks (2)). This is confirmed in examination of the control group of Welfare mothers (coefficient $r = 0{\cdot}021 \pm 0{\cdot}065$).

The standing rates are higher in the pregnant women than in the control groups taken by the same method, but are within the range of figures given by other workers; the exact duration of the standing period is not, however, recorded by these. Records of the standing rate in the present series were made during two consecutive minutes. The mean rates for the two periods are the same to two places of decimals. The second minute rate is given below.

	Obs.	Mean Pulse-rate. Standing Position.	Standard Deviation.
Pregnant cases	615	$90{\cdot}87 \pm 0{\cdot}31$	11·41
Female Controls.			
Laundry workers	49	$84{\cdot}22 \pm 0{\cdot}99$	10·36
Students	50	$79{\cdot}03 \pm 1{\cdot}08$	11·49
Students (Cripps)	115	$93{\cdot}29 \pm 0{\cdot}70$	11·19
Clerks (Cripps)	125	$87{\cdot}65 \pm 0{\cdot}06$	9·75

Exercise tests. At each attendance the pregnant patients were asked to carry out an exercise, as a means of testing the general capacity for exertion. A stationary stepping test was selected as the most convenient in application. The test was a light one, as it was thought undesirable to use any form of severe exertion that might be resented by the women in later months of pregnancy; it was, however, sufficiently strenuous to tax severely any case of partial cardiac decompensation.

A stool seven inches high was used, and the patient was required to step up and down. The feet were moved consecutively (right up, left up, right down, left down), so that the whole body weight was lifted and lowered to complete one step. Thirty steps were made in sixty seconds, the patient stepped in rhythm with a metronome, and the time was kept with a stop-watch. At the end of the test the patient sat down directly and the pulse was counted for two minutes, four half-minute counts being noted. The first ten-second count was recorded separately, and the maximum rate per minute calculated from this. The minimum rate during the period was calculated from the lowest half-minute count.

The normal response to the test used is a rise of pulse-rate to a maximum which is of only 10 to 15 seconds duration. This maximum is usually about half as much again as the previous rate, i.e. the rate increases from 80 to 120 per minute; a fall in pulse-rate follows. In a 'good response' the rate is slowed after the first 60 to 90 seconds to several beats below the resting rate; the fall is not always steady, for there is often a temporary drop followed by a secondary rise, and the final return may be delayed. No record of the time interval before this final return has been attempted; it has been shown by Pembrey (9) and others to depend on the duration and severity of the test.

There is no standard with which to compare the results of the test employed here, except the figures for the groups of controls tested by the same method, as the tests used by other workers are not precisely similar. The pulse-rates for the pregnant cases fall between the mean rates for the control groups: the difference ($2{\cdot}39 \pm 1{\cdot}31$) between the rates for the pregnant women and the laundry women is insignificant. So also is the difference ($1{\cdot}88 \pm 1{\cdot}43$) between the rates for the pregnant women and the students. In the pregnant cases there is no increase in the mean rates with the advance of pregnancy. The correlation of the minimum rate with the period of pregnancy is negative, but very small (correlation coefficient $r = -0{\cdot}095 \pm 0{\cdot}027$).

Pulse-rates before and after Exercise related to the Period of Pregnancy.

Weeks.		Pulse-rates (mean of all observations).			
		Sitting.	After Exercise.		
			Maximum.	Minimum.	Total in 2 min.
5–20		$82{\cdot}20 \pm 0{\cdot}89$	$121{\cdot}25 \pm 1{\cdot}08$	$83{\cdot}68 \pm 0{\cdot}84$	$182{\cdot}30 \pm 1{\cdot}68$
21–24		$81{\cdot}30 \pm 0{\cdot}99$	$121{\cdot}70 \pm 1{\cdot}20$	$77{\cdot}88 \pm 0{\cdot}93$	$174{\cdot}83 \pm 1{\cdot}97$
25–28		$84{\cdot}72 \pm 0{\cdot}74$	$122{\cdot}07 \pm 1{\cdot}00$	$82{\cdot}38 \pm 0{\cdot}77$	$182{\cdot}58 \pm 1{\cdot}53$
29–32		$86{\cdot}86 \pm 0{\cdot}72$	$122{\cdot}83 \pm 0{\cdot}99$	$81{\cdot}02 \pm 0{\cdot}77$	$183{\cdot}42 \pm 1{\cdot}51$
33–36		$84{\cdot}07 \pm 0{\cdot}69$	$121{\cdot}64 \pm 0{\cdot}98$	$81{\cdot}61 \pm 0{\cdot}75$	$186{\cdot}47 \pm 1{\cdot}41$
37–		$82{\cdot}91 \pm 0{\cdot}69$	$119{\cdot}90 \pm 0{\cdot}94$	$78{\cdot}58 \pm 0{\cdot}74$	$178{\cdot}72 \pm 1{\cdot}46$
	Obs.				
All Weeks	537	$83{\cdot}97 \pm 0{\cdot}31$	$121{\cdot}53 \pm 0{\cdot}42$	$80{\cdot}91 \pm 0{\cdot}32$	$181{\cdot}93 \pm 0{\cdot}64$
Laundry women	49	$84{\cdot}02 \pm 0{\cdot}90$	$119{\cdot}14 \pm 1{\cdot}24$	$82{\cdot}02 \pm 1{\cdot}02$	$184{\cdot}30 \pm 1{\cdot}98$
Students	50	$82{\cdot}30 \pm 1{\cdot}14$	$123{\cdot}41 \pm 1{\cdot}37$	$77{\cdot}13 \pm 1{\cdot}11$	$172{\cdot}74 \pm 2{\cdot}23$

The ratios of the pulse-rates after exercise to the resting rate have been examined in relation to the weight, but the correlation in both cases is very small, and supports the conclusion that the increase of weight in pregnancy does not adversely affect the exercise tolerance as determined by a light test.

Correlation of Exercise Response with Body Weight.

	Mean	Standard Deviation
Ratio $\frac{\text{minimum rate}}{\text{resting rate}}$	0·943	0·092
Ratio $\frac{\text{2-minute count}}{\text{resting rate}}$	2·166	0·209
Weight in kilos	61·16	7·960

Correlation of $\frac{\text{minimum rate}}{\text{resting rate}}$ with weight $= 0{\cdot}063 \pm 0{\cdot}032$.

Correlation of $\frac{\text{2-minute rate}}{\text{resting rate}}$ with weight $= 0{\cdot}082 \pm 0{\cdot}032$.

The total two-minute count and the minimum rate after exercise are both correlated with the previous resting rate. Correlation coefficients: between sitting rate and 2-minute count, $r = 0{\cdot}732$; between sitting rate and minimum rate, $r = 0{\cdot}727$.

Pulse-pressure and Pulse-rate product. The 'Cardiac Energy' Index. The value of this product was first suggested by Erlanger and Hooker (10) and has been maintained by many workers since. Stocks has recently examined the

index in young persons and adults. Cripps, in her report on efficiency tests in women, has not discussed the use of the pulse-pressure rate product, but this has been calculated from her tables and recorded below. The index up to the thirty-second week of pregnancy varies within the normal range, but falls in the following periods below the average normal mean, the chief factor contributing to the fall being the lowered pulse-pressure.

Pregnant Women.

Weeks of Pregnancy.	P. R. × P. P.	'Cardiac Energy' Index.
5–20	82·20 × 42·64	= 3505
21–	81·30 × 42·60	= 3463
25–	84·72 × 41·62	= 3526
29–	86·86 × 40·90	= 3553
33–	84·07 × 38·95	= 3275
37–	82·91 × 37·08	= 3074
All weeks	83·97 × 40·10	= 3367
Female Controls.		
Welfare mothers	83·60 × 45·31	= 3788
Laundry workers	84·02 × 45·72	= 3841
Students	82·30 × 41·34	= 3402
Cripps: Students	76·28 × 50·52	= 3854
Clerks	73·82 × 48·29	= 3565
Stocks, Adults male and female	Average value	= 3465

Discussion.

The results given in detail above show that among women of the working classes there is during pregnancy a lowered systolic pressure accompanied at first by a lowered diastolic pressure which rises in the later months to a higher level. These results are not in all respects in agreement with those of previous workers. Slemons and Goldsborough (3) in their ten cases found a mean systolic pressure of 127 mm. Hg. and a diastolic of 74 mm.; the systolic pressure is approximately 12 mm. above the mean (114 mm.) in this series, but the diastolic figures are in agreement. Vaux (4) finds that the blood-pressure is low and gives the systolic range from 100 to 125 mm. and the diastolic from 60 to 80 mm. He states, however, that the pressures are lower in the early months, and attributes this to a loss of vitality associated with nausea, vomiting, and insufficient food and drink. This is not supported by the present figures, in which very slight variations appear in the means for the successive periods: further, a study of individual cases in this series with exceptionally low blood-pressures proves that this may be present without vomiting, inanition, or other symptoms. The cause or causes producing the low systolic pressure must operate throughout pregnancy, and it will be seen from the post-natal records that the low pressure persists for three to six months, and reaches the lowest figure between two to four weeks after confinement. A fuller study of cases in the earliest weeks of pregnancy and after confinement would be of value in determining when the fall in systolic pressure first appears, and when the pressure returns to normal.

The extreme upper value of systolic pressure which will be exceeded in only 1 or 2 per cent. of normal women during pregnancy is calculated as

134 mm. Hg. Persistent values above this figure should be considered as possibly indicating early toxaemia, and call for careful investigation. Cases with high readings occur, in whom no other signs of abnormality can be found; the records of two such cases are given, one of them was seen again after confinement, when she still had raised pressures. They were young women aged 19 and 20 years, and the hyperpiesis was possibly 'congenital'.

The systolic pressure must be considered further in relation to the diastolic and pulse pressures. The lowered diastolic pressure in the earlier months produces the expected physiological adjustment by which the systolic and diastolic pressures tend to rise and fall together, and the pulse-pressure is thus kept at a fairly constant level in the normal individual. The rise of diastolic pressure which is a significant fact of the last three months of pregnancy is not related to any change in the systolic pressure. It is recognized that the diastolic pressure is usually higher when the subject is standing than in the sitting position; when standing, the return of the blood to the heart is carried out against the increased effect of gravity, and extra work is required to bring back the blood to the thorax; the rise of diastolic pressure appears to be the normal physiological response to this, and when absent the subject frequently shows evidence of maladjustment (Turner (11)). The mean rise of diastolic pressure in females on changing from a sitting to a standing position was found by Stocks to be 4·77 mm. Hg. He also notes that a fall of pulse-pressure generally accompanies the change, as the rise of systolic pressure is less than the diastolic or is absent; a fall of diastolic pressure together with a rise of systolic producing an increase of pulse-pressure on standing is rarely found. It is probable that the rise of diastolic pressure and fall of pulse-pressure in later pregnancy are to be attributed to a somewhat similar reaction, since at this time there is a relatively greater proportion of the total volume of blood to be returned to the thorax from the abdomen. Altered relations of intra-abdominal and intrathoracic pressures may also contribute to produce the change. This view is supported by the finding that the diastolic pressure returns to a normal figure immediately after delivery.

The resting pulse-rates of women as given by different workers vary considerably, and the rates of the pregnant women appear to be normal for their class; there is no increase with the advance of pregnancy, but rather a decrease which lessens the work performed by the heart. This diminution of cardiac work appears to be demonstrated by the 'cardiac energy index', which falls from a maximum in the period 29 to 32 weeks to the minimum in the period 37 to 40 weeks. It will be seen later to reach a lower value in the post-natal period. The application of this index has been studied by Stocks, who finds a high value in young persons during the period of rapid growth and a fairly steady average after 20 years, the value being the same for adults of both sexes. Macwilliam and Melvin (12) showed that the index was not applicable to pathological conditions as an estimate of cardiac output and velocity of flow, for high pulse-pressures may be present with a rapid pulse-rate together with defective mass movement of the blood. On the other hand, a lowered peripheral resistance or

a decrease in blood viscosity might lower the pulse-pressure and the index, though myocardial efficiency and the mass movement of the blood were fully maintained. The lowered index figure in later pregnancy appears to be associated with no failure of circulatory efficiency in the performance of moderate work, as judged by the exercise test. The minimum pulse-rate after exercise is considered to be the best test of exercise tolerance, and in every pregnant group except the first this minimum is from two to four beats below the resting rate. All the pulse records in the period 37 to 40 weeks are below those for the two previous 4-week periods; this is the more remarkable since the actual weight lifted and work done during the exercise is greater than in the earlier periods. Personal observation of the patients during the test conveyed the impression that little additional effort was required for its performance at this time.

The observations made in this inquiry cover a limited field only, and many questions relating to circulatory conditions in pregnancy arise which need to be answered by further investigation. The results show that in pregnancy there are but slight deviations from normal standards, and that such changes as occur tend to lessen the work of carrying on the circulation. This may perhaps be regarded as a physiological adjustment for the husbanding of resources rather than a restriction of output resulting from inability to meet excessive demands, for when increased effort is required it is met by a normal response.

Observations on Women during the First Six Months after Confinement.

Observations on these cases are more limited both in numbers and scope than those made during pregnancy. A total of 203 records is analysed in groups according to the length of time after the confinement, as the physical conditions at the beginning and end of the period differ widely.

Group.	Time after Confinement.	Obs.	Conditions of Examination.
1	From 48 hours to 7 days	56	In bed, reclining position
2	„ 7 days to 1 month	63	In bed, reclining, a few records taken in sitting position
3	„ 1 month to 3 months	46	In sitting position
4	„ 3 months to 6 months	38	In sitting position

No observations were made less than forty-eight hours after delivery, to allow a period for recovery from the physical fatigue of labour.

In the table have been set out for comparison the records for the 39th to 40th weeks of the pregnant group and those for women over six months after confinement who form the control group. Blood-pressure and pulse-rate observations only were made.

It is seen that there is no significant difference in the mean systolic pressure in the first week after confinement and the last weeks of pregnancy, but there is a considerable fall in the following weeks up to three months. The mean pressure for group 2 is 3·7 mm. below that for the last month of pregnancy and 9·17 mm. below the figure for the controls, and at three to six months it is still 4·18 mm. below the control figure. See Curve I, p. 387 and Table, p. 397.

Table of Blood-pressures and Pulse-rates of Post-natal Groups up to Six Months after Confinement compared with the Ninth Month of Pregnancy and with Controls.

	9th Month Pregnancy.	After Confinement. Group 1. From 48 hours to 7 days.	Group 2. 7 days to 1 month.	Group 3. 1 to 3 months.	Group 4. 3 to 6 months.	'Welfare Mothers' Controls over 6 months after Confinement.
Observations	107	56	63	46	38	113
Syst. Pr. mm. Hg.						
Lying	114·63	114·43 ± 0·82 s. d. 9·08	110·93 ± 0·95 s. d. 11·18	No obs.	No obs.	No obs.
Sitting	116·02	No obs.	No obs.	112·46 ± 1·08 s. d. 10·85	115·92 ± 1·38 s. d. 12·59	120·10 ± 0·65 s. d. 10·24
Diast. Pr. mm. Hg.						
Lying	78·75	74·50 ± 0·66 s. d. 7·33	73·12 ± 0·74 s. d. 8·76	No obs.	No obs.	No obs.
Sitting	78·94	No obs.	No obs.	75·24 ± 0·77 s. d. 7·72	76·55 ± 0·85 s. d. 7·78	74·74 ± 0·51 s. d. 8·01
Pulse Pr. mm. Hg.						
Lying	35·88	40·50 ± 0·77 s. d. 8·51	37·39 ± 0·68 s. d. 7·96	No obs.	No obs.	No obs.
Sitting	37·08	No obs.	No obs.	37·02 ± 0·86 s. d. 8·62	39·13 ± 0·98 s. d. 8·93	45·31 ± 0·58 s. d. 9·16
Pulse-rate per min.						
Lying	85·50	75·71 ± 1·08 s. d. 12·00	71·06 ± 0·89 s. d. 10·53	No obs.	No obs.	No obs.
Sitting	82·91	No obs.	No obs.	75·22 ± 1·04 s. d. 10·57	76·73 ± 1·17 s. d. 10·27	83·60 ± 0·92 s. d. 15·27
*P. P. × P. R.	3074	2866	2657	2785	3002	3788

* Pulse-pressure × pulse-rate product or 'cardiac energy' index.

The mean diastolic pressure for the first week after confinement is 4·25 mm. below that for the last month of pregnancy and is a normal figure, and during the whole period of six months the means show slight variations only, which are in the same direction as the larger variations of the systolic pressures. See Curve II, p. 387.

The mean pulse-pressure rises in the first week with the fall of diastolic pressure, but remains throughout the whole period at a low figure as the result of the persistently low systolic pressure.

The mean pulse-rates are low throughout in comparison with the rates (83 to 84) for the control groups of this series. A low rate is a well-known feature of the puerperium, and it is noticeable that the lowest rate, 71 per minute, is found not in the first week after delivery, but in the next period up to one month. From one to six months it is still low, though the numbers in these groups are small, and the probable errors large; considered with the figures given by other workers (73 to 76, see above) they fall within the normal range. See Curve III, p. 387.

The presence or absence of lactation and menstruation should be considered in a study of this period. During the first month after confinement practically all normal women have actively functioning breasts and normal menstruation is absent, and the conditions may be taken as uniform in this respect. Information was obtained from fifty-two cases seen between one and six months. Suckling, menses absent, 37; suckling, menses returned, 5; not suckling, 10.

Discussion.

There is a considerable departure from the normal standards of blood-pressure and pulse-rate in women up to six months after confinement. Within the first week there is a fall of 4·25 mm. Hg. in the mean diastolic pressure and a rise of 4·62 mm. in pulse-pressure. This fall of diastolic pressure is the most remarkable change in the first week; it is not to be ascribed to haemorrhage as the alteration is persistent and the mean figure is a normal one. It has been observed earlier that the diastolic pressures rise steadily during the last three months of pregnancy to a maximum in the last month, and it is reasonable to attribute the change to the enlarging territory of the circulation in the uterus and ovum, together with altered relations of intra-abdominal and intrathoracic pressures, and to regard it as an adjustment to the increased amount of work. Both the area of circulation and the intra-abdominal pressure are altered suddenly and permanently with delivery, and the fall of diastolic pressure and rise of pulse-pressure may be considered as the result.

The systolic pressure does not show a fall in the first week, but reaches the lowest figure, 111 mm., in the second period; it rises in each successive group, but is still below the control figure in group 4. The pulse-rates vary in the same direction, reaching the lowest figure in group 2. The lowest mean figures for all the records are reached in this group, but it is remarkable that they are but little higher in the following group up to three months after confinement. The 'Cardiac Energy' index varies with the pulse-rate and pulse-pressure, and is

consequently very low. The value of this index has been discussed above. The interpretation of these persistently low values during six months after pregnancy is of interest; they show that complete readjustment of cardio-vascular conditions is not obtained till after this time has elapsed. The post-natal periods need to be studied in more detail than is possible with the small number of cases here available.

Basal metabolic rate in pregnancy and in the post-natal period has been studied by Rowe, Alcott, and Mortimer (13) on a series of cases, and by Sandiford and Wheeler (14) on a single case with numerous observations. The variations reported are all within the range of normal figures from −12 to +8 per cent., but the variations appear to be consistently in the same direction. From the 32nd to the 40th weeks the rate increases steadily above that of the earlier weeks, reaching a maximum at full term. The increase is considered by Sandiford (14) to be completely accounted for by the metabolic rate of the developing foetus as calculated from its presumed weight and surface area. After delivery the rate falls promptly, the lowest figures are obtained, not immediately, but in about the fourth week; the rate then is lower than the pre-pregnancy rate, and is between −10 and −12 per cent.; a very gradual return to the normal is made, and this is only reached towards the end of six months (Sandiford). These findings require confirmation, but if they are accepted the post-natal metabolic rate tallies well with the low figures for pulse-rates and blood-pressures; they show a considerable slowing down of the physiological processes with a maximum effect at three or four weeks and a relatively slow rate of recovery which is probably not complete under six months.

Conclusions.

1. The average systolic blood-pressure of healthy women during pregnancy is lower than the average of non-pregnant women, also the average deviation during pregnancy is less and the range is consequently slightly smaller. Changes during the course of pregnancy show a tendency to a lower pressure in the middle period than in the earlier weeks, and there is a slight but significant rise in the last three months. Any considerable rise is to be associated with the onset of a toxic condition. The mean pressures show no relation to age except in the age group over 35 years, in which the mean is significantly higher.

2. The mean diastolic pressure during pregnancy is not significantly different from that of non-pregnant women. The general mean must, however, be considered in relation to the changes occurring with the course of pregnancy which are of definite significance. During the first six months the mean pressures are below the general mean, and there is a steady rise from the seventh month to a maximum in the last month, which is higher than the mean for non-pregnant women.

3. The pulse-pressure is lower than that of non-pregnant women, and falls with the advance of pregnancy.

4. The pulse-rate during pregnancy is not significantly altered from the normal. The difference between the sitting and standing rates is within the range of the normal increase. The pulse-rates show no significant correlation with the period of pregnancy.

5. An exercise test is well performed, and the pulse-rates after exercise are not significantly different from those of controls; in the last months of pregnancy the mean rates after exercise are below those of the preceding periods. The rates after exercise are highly correlated with the resting rate.

6. The 'cardiac energy' index falls in later pregnancy below the normal figure, but the application of this index is considered to be of doubtful value.

7. There is no evidence to be found in this work of embarrassment of the circulation during the later months of pregnancy.

8. The mean systolic pressure during the first week following parturition remains at the same level as in the ninth month of pregnancy, but reaches a low mean figure, 111 mm. Hg., subsequently, and returns very slowly to the control figure.

The diastolic pressure falls from the raised figure of the last weeks of pregnancy to a normal figure, 74 mm. Hg., in the first week, and varies but little subsequently.

Pulse-pressure rises in the first week to 40 mm. Hg. and then falls, remaining below the control figure up to six months.

9. The mean resting pulse-rate following parturition is lower than at any period of pregnancy; the lowest rate, 71 per minute, occurs after the first week, namely from the second week to the end of the first month. The rate remains below the control figure throughout.

10. Studies in basal metabolism in pregnancy and the post-natal period published by other workers are referred to, and the coincidence of the lowest metabolic rate as found by others and of the minimum pulse-rate and blood-pressures as found in this investigation in the second to the fourth weeks after confinement is pointed out. These minimum metabolism rates are below those for non-pregnant cases.

11. The product pulse-pressure × pulse-rate has been examined. After confinement, low values are obtained, which persist up to six months.

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Ante-Natal Observations

Normal Pregnant Women.

Period of Pregnancy in Weeks.

Blood-pressures in mm. Hg.	All Weeks.		5–20. (67 Cases.)	21–24. (54 Cases.)	25–28. (91 Cases.)	29–32. (102 Cases.)	33–36. (103 Cases.)	37– (107 Cases.)
	Mean.	S. D.	Mean.	Mean.	Mean.	Mean.	Mean.	Mean.
No. of cases 524								
Age in years	28·09	5·98						
Weight k.g.	—	—	55·90	59·45	59·53	62.59	62·38	63·95
Sys. P. Lying	113·28 ± 0·19	9·43	113·37 ± 0·68	113·27 ± 0·75	112·96 ± 0·62	112·88 ± 0·62	112·57 ± 0·61	114·63 ± 0·75
Sitting	114·07 ± 0·26	8·72	113·41 ± 0·72	112·16 ± 0·80	111·93 ± 0·62	114·83 ± 0·58	114·60 ± 0·58	116·02 ± 0·57
Dias. P. Lying	73·16 ± 0·24	8·45	70·40 ± 0·61	70·22 ± 0·67	70·76 ± 0·56	72·17 ± 0·56	75·25 ± 0·56	78·75 ± 0·56
Sitting	73·82 ± 0·24	8·18	70·77 ± 0·69	69·57 ± 0·76	70·32 ± 0·57	73·93 ± 0·55	75·66 ± 0·55	78·94 ± 0·54
Pulse P. Lying	—	—	—	—	—	—	—	35·88
Sitting	40·10 ± 0·25	8·30	42·64	42·59	41·61	40·90	38·94	37·08
Pulse-rates per minute.								
No. of cases 501								
Lying	84·53 ± 0·29	10·64	—	—	—	—	—	85·50
Sitting	83·97 ± 0·31	10·35	82·20 ± 0·89	81·30 ± 0·99	84·72 ± 0·74	86·86 ± 0·72	84·07 ± 0·69	82·91 ± 0·69
Standing 2nd min.	90·87 ± 0·31	11·41	—	—	—	—	—	—
P. P. × P. R.	3367	—	3505	3463	3526	3553	3275	3074
Pulse-rates after Exercise.								
No. of cases 537								
Maximum (6 × 1st 10 secs.)	121·53 ± 0·42	15·29	121·25 ± 1·08	121·70 ± 1·20	122·07 ± 1·00	122·83 ± 0·99	121·64 ± 0·98	119·90 ± 0·94
Minimum (within 2 min.)	80·91 ± 0·32	11·86	83·68 ± 0·84	77·88 ± 0·93	82·38 ± 0·77	81·02 ± 0·77	81·61 ± 0·75	78·58 ± 0·74
Total 2 min.	181·93 ± 0·64	22·58	182·30 ± 1·68	174·83 ± 1·97	182·58 ± 1·53	183·42 ± 1·51	186·47 ± 1·41	178·72 ± 1·46

S. D. = Standard deviation. Dias. P. = Diastolic pressure. P. P. × P. R. = Pulse-pressure × pulse-rate product.
Sys. P. = Systolic pressure. Weeks = Weeks of pregnancy.

Post-Natal Observations

Normal Women after Confinement.

Relation of Date of Observation to Confinement.

Blood-pressures in mm. Hg.	Under 7 Days. (56 Cases.)		7 Days to 1 Month. (63 Cases.)		1 to 3 Months. (46 Cases.)		3 to 6 months. (38 Cases.)	
	Mean.	S. D.	Mean.	S. D.	Mean.	S. D.	Mean.	S. D.
Age in years	—	—	—	—	—	—	28·27	5·50
Sys. P. Lying	114·43 ± 0·82	9·08	110·93 ± 0·95	11·18	—	—	—	—
Sitting	—	—	—	—	112·46 ± 1·08	10·85	115·92 ± 1·38	12·59
Dias. P. Lying	74·50 ± 0·66	7·33	73·12 ± 0·74	8·76	—	—	—	—
Sitting	—	—	—	—	75·24 ± 0·77	7·72	76·55 ± 0·85	7·78
Pulse P. Lying	40·50 ± 0·77	8·51	37·39 ± 0·68	7·96	—	—	—	—
Sitting	—	—	—	—	37·02 ± 0·86	8·62	39·13 ± 0·98	8·93
Pulse-rates per min.								
Lying	75·71 ± 1·08	12·00	—	—	—	—	—	—
Sitting	—	—	71·06 ± 0·89	10·53	75·22 ± 1·04	10·57	76·73 ± 1·17	10·27
P. P. × P. R.	2866	—	2657	—	2785	—	3002	—

S. D. = Standard deviation. Dias. P. = Diastolic pressure. P. P. × P. R. = Pulse-pressure × pulse-rate product.
Sys. P. = Systolic pressure. Weeks = Weeks of pregnancy.

Control Cases

Normal Women. Non-Pregnant.

Blood-pressures in mm. Hg.	113 Mothers at Welfare Centre over 6 months after Pregnancy.		49 Laundry Workers.		50 Medical Students.	
	Mean.	S. D.	Mean.	S. D.	Mean.	S. D.
Age in years	29·58	5·37	28·36	6·94	21·9	—
Weight k. g.	58·03	—	56·23 ± 0·80	—	—	—
Sys. P. Lying	—	—	—	—	—	—
Sitting	120·10 ± 0·65	10·24	123·74 ± 1·25	12·96	119·38 ± 1·06	11·21
Dias. P. Lying	—	—	—	—	—	—
Sitting	74·74 ± 0·51	8·01	78·54 ± 0·70	7·28	77·81 ± 0·62	6·52
Pulse P. Lying	—	—	—	—	—	—
Sitting	45·31 ± 0·58	9·16	45·72 ± 1·05	10·85	41·34 ± 1·02	10·77
Pulse-rates per min.						
Sitting	83·60 ± 0·92	15·27	84·02 ± 0·90	9·42	82·30 ± 1·14	12·07
Standing 2nd min.	—	—	84·22 ± 0·99	10·36	79·03 ± 1·08	11·49
P. P. × P. R.	3788	—	3841	—	3402	—
Pulse-rates after Exercise.						
Maximum (6 × 1st 10 secs.)	No observations		119·14 ± 1·24	12·98	123·41 ± 1·37	14·46
Minimum (within 2 min.)	—	—	82·02 ± 1·02	10·67	77·13 ± 1·11	11·73
Total 2 min.	—	—	184·30 ± 1·98	20·73	172·74 ± 2·23	23·56

S. D. = Standard deviation. Dias. P. = Diastolic pressure. P. P. × P. R. = Pulse-pressure × pulse-rate product.
Sys. P. = Systolic pressure. Weeks = Weeks of pregnancy.

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THE SIGNIFICANCE OF THE POLYNUCLEAR (COOKE) AND SCHILLING LEUCOCYTE COUNTS[1]

By A. PINEY

Arneth was the first to suggest that the ordinary total and differential leucocyte counts were not capable of giving a sufficiently delicate indication of haematological changes. He started from the universally admitted facts that neutrophilic granular leucocytes with single round nuclei (myelocytes) and with simple indentation of single round neuclei (metamyelocytes) are less mature than ordinary polymorphonuclear leucocytes with segmented nuclei. He contends that cells with two nuclear segments are less mature than those with three, and so on. He, therefore, classifies the neutrophilic granular leucocytes into five classes according to the number of lobes, and states that the normal numbers are about :

Class I	. . . . .	5 per cent.
Class II	. . . . .	35 „
Class III	. . . . .	47 „
Class IV	. . . . .	17 „
Class V	. . . . .	2 „

He goes farther and subdivides these classes into many groups based on the shape of the nuclear lobes, but this does not really concern us here. It is, however, important to note that Class I is subdivided into M cells (myelocytes with simple round nuclei), which are absent from normal blood; W cells with single, slightly indented nuclei, which are very rarely found in normal blood; and T cells with deeply indented single nuclei, which form the 5 per cent. of neutrophils of Class I normally present in the blood.

Unfortunately there is no clear description of the characters by which a lobe is to be recognized and, therefore, different observers may obtain widely differing results from examination of the same film: even the same observer will obtain varying results until he has had a very large amount of practice. Furthermore, pathological conditions, particularly infective states, are well known to cause distinct alterations in the polymorphs, which may then appear to have fewer lobes than is really the case.

Cooke has modified the Arneth method and has clearly indicated the character by which a lobe can be recognized. 'If there is any band of nuclear material except a chromatin filament connecting the different parts of a nucleus, the nucleus cannot, for the purpose of the count, be said to be divided.' This

[1] Received November 28, 1928.

method of classification is easy to follow, even in pathological states. Cooke's normal figures differ from those of Arneth and are as follows:

Class I	12 per cent.
Class II	25 „
Class III	44 „
Class IV	15 „
Class V	4 „

Any increase in the number of cells in the lower classes is termed, both by Arneth and Cooke, a 'shift to the left', and the opposite condition, which is much rarer, is a 'shift to the right'. Cooke states that the greatest shift to the left found in health is:

Class I	15 per cent.
Class II	34 „
Class III	40 „
Class IV	11 „
Class V	nil.

The greatest shift to the right compatible with health is:

Class I	9 per cent.
Class II	24 „
Class III	47 „
Class IV	17 „
Class V	3 „

For the sake of concise expression, Cooke has introduced the use of the 'weighted mean'. He multiplies the number of cells in Class I by 1, in Class II by 2, and so on. The numbers so obtained are added together and divided by the number of cells, viz., 100. The average weighted mean in health is, therefore, 2·74, the highest 3·11 and the lowest 2·47.

It will be noticed that Cooke does not subdivide the cells of Class I, and although he would no doubt record the presence of myelocytes, their presence would not influence the weighted mean. For example, if, which is extremely improbable, one ever met a case with 100 per cent. of cells in Class I, the weighted mean would be 1·00 whether the nuclei of these cells were round, slightly indented, or deeply indented.

Schilling adopts a different method of classifying the neutrophilic leucocytes. Both Arneth and Cooke count a hundred neutrophils and then arrange the cells in their classes as percentages of the neutrophils, but Schilling expresses the different types as percentages of the total leucocytes. His classification is even simpler than that of Cooke. He recognizes myelocytes with simple round nuclei, 'young forms' with slightly indented nuclei, 'band forms' with elongated deeply indented nuclei, which form about 4 per cent. of the total leucocytes in health, and cells with segmented nuclei, which form about 63 per cent. of the total leucocytes in health.

It is clearly impossible, at least for clinical purposes, to use the Arneth

count in all its complexity. The 'polynuclear count' of Cooke is open to the objection that the cells of Class I are not subdivided according to their degree of nuclear complexity, i. e. of maturity. Schilling's method has the defect that, although it recognizes the importance of accurately classifying the mononuclear forms of neutrophilic granular leucocytes, it does not attach any importance to the degree of nuclear complexity of the cells with segmented nuclei.

It seems, therefore, that both the Cooke and the Schilling method could supply different information, and the purpose of the present paper is the discussion of the results obtained in a variety of cases by using both methods. It is very little more laborious to perform both counts while doing the ordinary differential count of the leucocytes than it is to do only one of them.

The whole difficulty arises in connexion with Class I. Cooke contends that about 15 per cent. of the neutrophils belong to Class I, whereas Schilling finds only about 6 per cent. in this class. If it can be shown that the number of 'band forms' and even of 'young forms' can increase without being associated with an increase in the number of cells in Cooke's Class I, it will have to be admitted that the Schilling count may, in some circumstances, be more delicate than the polynuclear count of Cooke.

The first cases investigated were women who had had complete amputation of the breast for carcinoma and were being treated with X-rays. The first chart shows the 'weighted means' of such a case before and during after-treatment. It will be noticed that the weighted mean at first falls and then rises to a level higher than that found before treatment. Incidentally, it may be mentioned that of all the twenty cases of this series, not one was found with a weighted mean as high as Cooke's normal figures, although, in apparently healthy persons, Cooke's normals could be confirmed. The second chart shows the percentages of cells with segmented nuclei, of band forms and of young forms. It will immediately be obvious that there is a steady but slight rise of band forms throughout the period of treatment, even at a time when the weighted mean has risen. Young forms, which at first were absent, appear in the later stages, although in very small numbers. Now, a high weighted mean should imply a fairly high degree of average nuclear complexity, but, in the present case, the rise of the weighted mean, although associated with such a high average, is also accompanied by an increase of more immature cells, i. e. there is a shift to the right of the Cooke count, and a shift to the left of the Schilling count.

The third and fourth charts show the fallacy of using only the polynuclear count in a severe case of septic infection of the cervix in a woman who had been treated with X-rays after hysterectomy for sarcoma of the uterus. Here, when the infection was at its height, the weighted mean was extremely low. For some days it remained fairly steady, with, however, one slight rise, but in spite of this, the number of young forms was markedly increasing without influencing the polynuclear count. Chart V shows the percentages of the different types of neutrophils, according to Cooke, and it is obvious that such a chart is very difficult to interpret without very careful examination.

Summary of Cases

No.	Name.	Diagnosis.	'Band' Forms.		Weighted Mean.		Treatment and number of treatments before last Blood Examination.	Remarks.
			Before Treatment.	After Treatment.	Before Treatment.	After Treatment.		
			%	%				
1	Mr. G.	Carcinoma testis	9·0	7·5	2·04	2·41	X-rays 2	The first method shows practically no change, whereas the second indicates great increase of maturity
2	Mrs. S.	C. mammae (operation)	4·0	4·7	2·44	2·16	X-rays 2	The first method shows no change, whereas the second shows decreased maturity of the cells
3	Mrs. Th.	C. mammae (operation)	3·0	8·0	1·78	2·16	X-rays 11	The first method shows presence of more immature cells after treatment, whilst the second shows general increase of maturity
4	Mrs. A.	C. mammae (operation)	6·0	4·0	2·24	2·48	X-rays 3	More or less agreement between the two methods, but the 'shift to the right' of the second is greater
5	Mrs. G.	C. mammae (operation)	nil	3·0	2·22	2·36	X-rays 10	Dissimilar changes
6	Mrs. P.	C. cervicis (operation)	1·7	6·0	2·04	2·38	X-rays 12	Dissimilar changes
7	Mrs. B.	C. mammae (operation)	4·3	4·3	2·24	2·38	X-rays 11	One method shows no change, whilst the other shows a 'shift to the right'
8	Mrs. C.	C. mammae (operation)	2·7	4·0	1·99	2·59	X-rays 7	Dissimilar changes
9	Mrs. Pa.	C. mammae (inoperable)	7·0	3·0	1·89	2·44	X-rays 7	More or less similar changes: at any rate both in the same direction
10	Mrs. Cl.	Acute rheumatism	3·8	8·0	2·05	2·36	Salicylates	Changes in opposite directions
11	Mrs. J.	C. mammae (inoperable and fungating)	5·0	14·0	2·06	2·14	X-rays 5	Changes in opposite directions
12	Mrs. Ba.	C. mammae (operation)	4·0	3·0	2·29	2·66	X-rays 2	Only the second method shows a change
13	Mrs. Bu.	C. cervicis (inoperable)	7·3	8·0	2·16	2·16	X-rays 2	Both methods agree in absence of change
14	Mrs. O'D.	Lymphadenoma	3·6	23·0	1·44	1·86	X-rays 7	Extreme disagreement
15	Mr. G.	Retro-peritoneal tumour	6·0	10·3	2·20	2·16	X-rays 2	Agreement
16	Mrs. B.	C. mammae (operation —sinus)	4·7	13·0	1·51	2·02	X-rays 7	Changes in opposite directions
17	Mrs. McA.	C. mammae	1·0	5·5	2·07	2·35	X-rays 6	Changes in opposite directions

The sixth and seventh charts show the same points in a case of Hodgkin's disease treated with X-rays.

Conclusions.

The Arneth count as modified by Cooke is a delicate index of leucocytic variation, but unless supplemented by the method of Schilling is unable to show the finest details. The Schilling count, unless used in conjunction with Cooke's polynuclear count, is also defective, particularly in showing fine degrees of shift to the right.

A complete blood count should, therefore, include both these methods in addition to the usual examinations.

This work was financed by the British Empire Cancer Research Committee as a part of its scheme for the investigation of the action of X-rays.

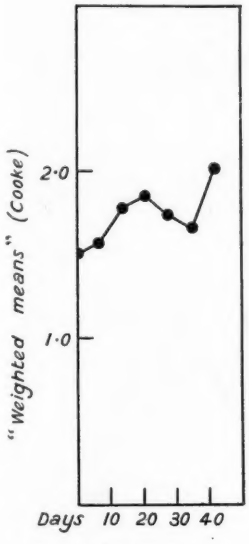


CHART I.

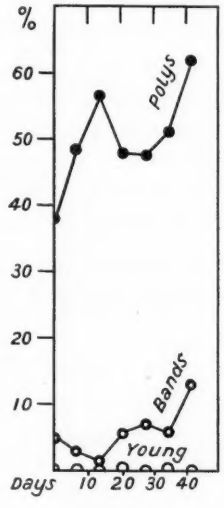


CHART II.

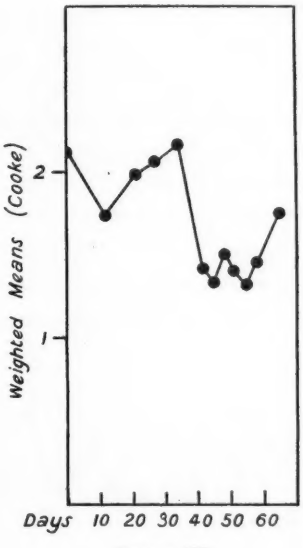


CHART III.

Chart I. This shows the 'weighted means' of the Arneth count as modified by Cooke.

The patient was an elderly woman from whom a carcinoma of the breast had been removed seven weeks earlier.

It will be noticed that there is at first a fairly steady rise of the weighted mean, and, in spite of a later drop, the last value is distinctly higher than the first. Such a chart would suggest that there is a more or less steadily progressive increase of average maturity of the neutrophilic granular leucocytes.

The small vertical lines at the bottom of the chart indicate the days on which X-ray treatment was given.

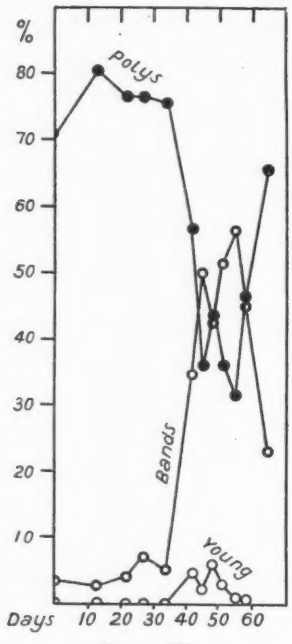


CHART IV.

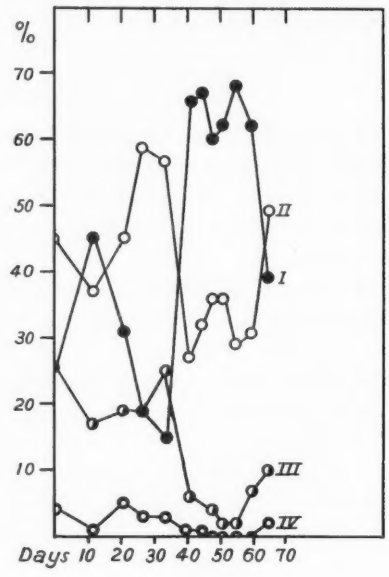


CHART V.

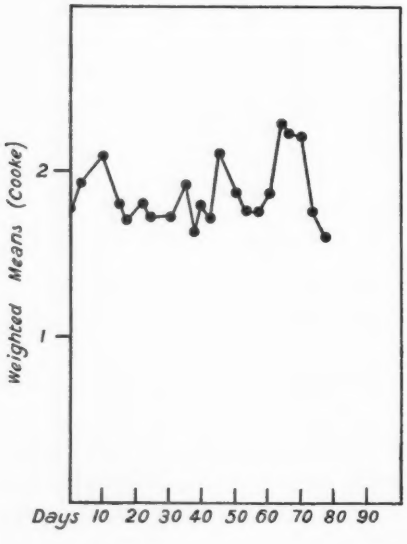


CHART VI.

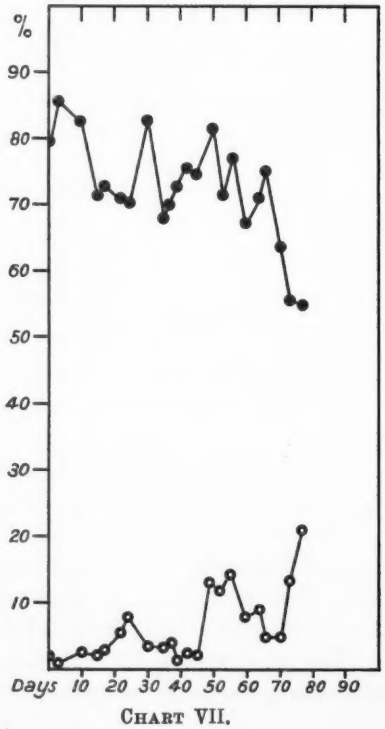


CHART VII.

Chart II. This was prepared from the same case. It is clear that there is a steady rise in the number of slightly immature neutrophils ('band forms') throughout the period of treatment. In other words, there is a slight tendency to increasing immaturity of the neutrophilic blood-picture. The use of the 'weighted mean' or of this method (due to Schilling) alone is, therefore, not capable of giving all the information needed.

The small vertical lines at the top of the chart indicate the days on which X-ray treatment was given.

Chart III. The 'weighted means' found in the case of severe sepsis mentioned in the text. The small vertical lines at the bottom indicate X-ray treatment. The onset of the sepsis is shown by the sharp fall of the line.

Chart IV. Here the mature neutrophils (polymorphs), 'band forms' and young forms are separately shown and a much clearer insight into the progress of the infection is obtained than is the case with the use of the 'weighted means' alone.

Chart V. This shows each of the types of neutrophil (according to Cooke) separately, and it is obvious that such a chart is much too complicated for clinical use.

Chart VI. The 'weighted means' from a case of lymphadenoma treated with X-rays (indicated by the small vertical lines at the bottom of the chart). The excursion of the line indicating the 'weighted means' does not give so good an idea of the changes in the neutrophilic blood-picture as do the lines indicating mature neutrophils and 'band forms' as shown in Chart VII.

Chart VII. The upper line indicates the percentage of mature neutrophils and the lower that of 'band forms' in the same case as that shown in Chart VI.

PRIMARY CARCINOMA OF THE LUNG[1]

By SAMUEL LEVY SIMPSON

This study of primary carcinoma of the lung is divided into two main sections. The first consists for the most part of a study of the clinical aspects of 139 cases which were admitted to the London Hospital between 1907 and 1925, and in all of which primary carcinoma of the lung was found *post mortem*. A preliminary note on the main features of the pathology of the condition is included, with especial reference to those features that have direct clinical significance. The second part deals with the increased incidence of primary carcinoma of lung, a consideration of its real or apparent nature, and a discussion on the aetiology of the disease. An appendix includes notes on a few cases illustrating the diagnostic and aetiological points discussed in the main part of the paper.

Pathology.

Primary carcinoma of the lung cannot be diagnosed with certainty on macroscopic examination alone. In particular one must exclude tumours of the thymus and thyroid, endotheliomata of the pleura, lymphogranulomata, lymphosarcomatosis, intrathoracic sarcomata, primary carcinoma of the oesophagus with extension into the lungs, and secondary malignant disease of the lung with an inconspicuous primary.

The appearance of tumours of the thymus and thyroid may be very deceptive on macroscopic examination, the lungs often being extensively involved by direct spread or by numerous metastases. Endotheliomata of the pleura are rare, there being only three cases in the period under investigation, namely 1907 to 1925. Lymphogranulomata and lymphosarcomatosis occasionally simulate carcinoma of the lungs closely, and may extend from the glands into the lungs and bronchi, thus producing bronchiectasis. There was only one case of intrathoracic fibrosarcoma in the period 1907 to 1925. Carcinoma of the oesophagus in the late stages may penetrate into the lungs or bronchi, an oesophageal-bronchial fistula thus being produced. The reverse process may occur. Secondary malignant disease of the lung with a distant primary focus occurs frequently, the lung acting as a filter through which all venous blood must pass before being distributed to other organs. Unlike primary carcinoma of the lung, these secondary growths tend to be scattered diffusely throughout the lungs.

Professor Turnbull has for many years held the view that primary malignant disease of the lungs and bronchi are nearly all carcinomata, and that the so-called

[1] Received December 5, 1928.

'oat-celled sarcomata' (also termed lymphosarcomata, mediastinal sarcomata, lymphosarcomata of the mediastinum) are in reality true carcinomata. Further, it appears probable that both the obvious carcinomata and the oat-celled carcinomata nearly all arise from the bronchi. It is of interest to note that Pässler (1) as long ago as 1896 concluded from an examination of the literature that 'in the majority of cases it can be shown that the new growth has its origin in the bronchial system, and further that no incontrovertible proof is forthcoming as to the existence of carcinoma arising from the alveolar tissue of the lung proper'. Many observers to-day in America and on the Continent (Barron (2), Kikuth (3)) classify their carcinomata as those arising from (*a*) the columnar epithelium lining the bronchi, (*b*) the mucous glands of the bronchi, (*c*) the flattened alveolar epithelium. Although possibly a correct theoretical classification, the polymorphism of the cells, which is a characteristic of these tumours, renders such division impossible in the majority of cases.

Professor Turnbull's views on the carcinomatous nature of the oat-celled tumours are confirmed by the investigations of Barnard (4) and Shennan (5).

Since the oat-celled tumours form a large proportion of intrathoracic tumours, it is of interest to give a brief *résumé* of the evidence in favour of their being carcinomata. Macroscopically the oat-celled tumours may be indistinguishable from a typical carcinoma, although characteristically they tend to be softer, to be more extensively necrosed, and to invade the mediastinum extensively, so as to constitute a large mediastinal mass with an adjacent small mass surrounding a bronchus in one hilum. In the typical carcinomata, on the other hand, the growth is usually firmer and more definitely acinar, whilst the main mass is in close relation to a bronchus. This differentiation is by no means constant, and no great reliance can be placed on macroscopical differentiation. Microscopically the typical carcinomata usually consist of several types of large cells: columnar, columnar mucous, cubical, polygonal, spherical, squamous, and additional varieties of intermediate forms. The oat-celled tumours consist mainly of small oval cells with scanty cytoplasm resembling oat grains. The nuclei are oval and deeply stained. Their classification as carcinomata, however, depends partly upon the absence of formation of intercellular fibrils or any other matrix, but chiefly on the fact that careful examination of many sections will reveal small areas in which the cells have definite epithelial characters, or in which the cells tend to take on a definite epithelial arrangement. In almost all examples the cells in the periphery of the acinar masses are small, narrow, columnar cells. Usually there are in places groups of larger columnar and polygonal cells, and possibly all grades of cells ranging from columnar to the small oat type. The cells in these groups tend to be polygonal and arranged in solid trabeculae or to be cubical or columnar and arranged around a lumen. The arrangement of the cells may even resemble that of the deeper layers of the bronchial epithelium. An additional observation of importance is the frequent presence of typical 'oat-cells' in sections of an obvious and accepted bronchial carcinoma. A secondary deposit from a large-celled tubular or squamous primary growth may consist

entirely of small 'oat cells'. Finally, a review of a large number of cases shows that between the typical large-celled squamous or tubular carcinoma on the one hand and the 'oat-celled' growth on the other, there are growths in which the preponderating cell is of various intermediate sizes. These growths, composed of intermediate sizes, are obviously carcinomata, and frequently suggest basal-celled carcinoma. It is significant that the oat-cell type of tumour does not arise elsewhere in the body either in lymphatic glands or in connective tissue.

The true carcinomatous nature of these oat-celled tumours is now recognized in this country, on the Continent, and in America. In this series of 139 cases 76 were of the oat-cell variety.

Of interest because of its rarity was a carcinomatous embryoma that occurred in a lad of 18. It consisted of a very large mass of cystic embryoma and degenerate medullary carcinoma filling the right pleural cavity and completely compressing the whole of the right lung.

The right and left lungs were affected with equal frequency, 69 of the cases occurring in the right lung and 70 in the left. The upper lobe was more frequently involved than the lower (upper 41, lower 29, indeterminate 67).

Metastases.

Metastases occur in the majority of cases, and in both the oat-cell type and the more obvious carcinomata metastases may be widespread and extensive. This may occur even with a small latent primary focus, the main signs and symptoms being due to the metastases. Metastases may occur quite early and may give the first indication of the disease.

The following table indicates the frequency with which various parts of the body are affected.

Metastases (139 cases).

Regional glands	104	Thymus	1
Extrathoracic glands	70	Muscle	8
Pleura	31	Skin	4
Lung	16	Diaphragm	9
Liver	45	Parotid gland	1
Suprarenals	41	Brain	19
Pancreas	25	Spinal cord	1
Kidneys	14	Vertebrae	29
Peritoneum	12	Femur	21
Intestines	8	Ribs	15
Spleen	5	Sternum	8
Stomach	2	Skull	5
Prostate	1	Pelvic bones	4
Thyroid	4	Humerus	2
Tonsil	2	Clavicle	1

It will be seen that glands are affected in the majority of cases.

Metastases occurred in the parietal pleura in 31 cases, but the pleura was also involved by direct spread in 9 cases. Metastases occurred in the lung, apart from direct spread of the primary growth, in only 16 cases.

Of the viscera the liver and suprarenals were the favourite sites, and the pancreas was also frequently involved.

The brain was affected in 19 cases, the occurrence of intracranial metastases being of great clinical significance. They may occur in the cerebrum or cerebellum, and may be single or multiple. Of the 19 cases, 11 were in the cerebrum, 4 in the cerebellum, and 4 in both cerebrum and cerebellum.

The skull was involved in only 5 cases.

The vertebral column, however, was affected in no less than 29 cases, in 7 of which signs of a cord lesion (such as paraplegia) were produced by pressure of the growth on the cord.

In only one case was the spinal cord itself the site of a metastasis, and in this case there was also a metastasis in the cerebellum.

Pathological Complications of Carcinoma of the Lung (139 cases).

The growth itself may undergo degenerative necrosis, haemorrhagic purulent infiltration, and abscess formation.

Pleura. Pleural effusions occurred in 39 cases, of which 9 were purulent (empyemata), 10 sanguinous, and 20 clear. Metastases occurred in the pleura in 31 cases and the pleura was directly infiltrated in 9 cases. Apart from these cases dry fibrinous pleurisy occurred in a general or localized form in no less than 51 cases. Thus it is seen that the pleura is involved in one form or another in the majority of cases.

The lungs. Bronchitis, broncho-pneumonia, bronchiectasis, collapse, gangrene, abscess formation, emphysema, and fibrosis may all occur. Partial or complete occlusion of the lumen of a large bronchus occurred in no less than 78 cases, and in the majority of these bronchiectasis and broncho-pneumonia were present. Abscesses occurred in 16 cases; the majority of these appeared to be of bronchiectatic origin, but in three cases multiple abscesses resulted from the breakdown of large areas of pneumonic consolidation, and in one case the abscess resulted from necrosis of the growth itself. Not infrequently an abscess was of very large size, and in three cases the abscess was drained after resection of a rib, two of the cases being mistaken for empyemata.

It is of interest to note that in no case of bronchiectasis did cerebral abscess occur as a complication.

Pericardium. The pericardium was directly invaded by the growth in no less than 62 cases, of which 21 developed pericardial effusions.

Oesophagus. The oesophagus was invaded in 17 cases, and in a further 6 cases the oesophagus was compressed or kinked.

Involvement of blood-vessels. Thrombosis occurred in 24 cases, the superior and inferior vena cava, innominate, internal jugular, axillary, iliac, and femoral veins being involved. Thrombosis of veins occurred almost as frequently in the lower as in the upper extremities, but, in addition to this, direct invasion and obstruction of the superior vena cava by growth occurred in no less than 16 cases.

The inferior vena cava was directly invaded by growth in only one case. In two cases of intracranial neoplasm the left lateral sinus and right retinal veins were thrombosed, the latter being associated with the sudden onset of blindness in one eye.

The pulmonary vessels were frequently affected both by thromboses and direct invasion of growth.

Signs and Symptoms of Carcinoma of the Lung.

Age. Carcinoma of the lung may occur at almost any age, the youngest in the series here investigated being 13 years of age and the oldest 77. The average age was 48 years, the majority of cases occurring between 40 and 68. Thus:

70–80 years	4 cases
60–70 „	21 „
50–60 „	45 „
40–50 „	41 „
30–40 „	18 „
20–30 „	6 „
10–20 „	4 „

Sex incidence. Of 139 cases, 111 were males and 28 females, that is 4 males to 1 female, as compared with an approximately equal proportion of males and females for all cases admitted to the hospital in the period under investigation. Duguid (6) finds an even higher proportion of males, although the majority of observers (Schmoller (7), Ferenczy and Matolcsy (8), Adler (9), Briese (10), Kaufmann (11), Ewing (12), Fishberg (13), Moses (14)) find the proportion of males to females to be about 3 to 1.

Onset. The onset may be sudden or insidious. Thus it may closely simulate an acute pneumonia or pleurisy, or, on the other hand, may be treated for many months as chronic bronchitis. Almost any one of the numerous signs and symptoms may be the first indication of the disease, as will be shown in the more detailed consideration. It may so happen, however, that the disease itself is latent and unobserved, until a metastasis manifests itself, often dramatically, as for example in convulsions due to a cerebral metastasis.

Duration. The average duration was seven months, the shortest in this series being only three days, while the longest was four years (2 cases). There were only 7 cases with a history of two years or longer, and 11 cases had a history of six weeks or less. Both short and long duration may be associated with all ages. Of the cases of especially long duration, however, the majority occurred in elderly patients.

Statistics of Main Symptoms and Signs.

In 139 cases investigated and confirmed at post-mortem the frequency of symptoms and signs was as follows:

Cough in	92 cases
Pain in	89 „
Wasting in	72 „
Dyspnoea in	70 „
Sputum in	70 „
Pyrexia in	54 „
Haemoptysis in	50 „
Clinical secondary deposits in	33 „
Cyanosis in	29 „
Dilated veins in	27 „
Oedema in	25 „
Laryngeal paralysis in	24 „
Night sweats in	24 „
Dysphagia in	15 „
Vomiting in	15 „
Clubbing of fingers in	9 „

Cough. Cough occurs in the majority of cases, although it may be absent throughout the course of the illness. It is often a dry cough to commence with, but sputum usually occurs at some stage of the disease.

The cough may have no special characteristics, being identical with that of chronic bronchitis and often merely due to the associated bronchitis.

In many cases, however, severe paroxysms of coughing are a characteristic feature of the condition. The paroxysms may cause intense discomfort, may be associated with a feeling of suffocation, and are sometimes described as agonizing in character. The paroxysms are often due to pressure on the trachea or large bronchi, with or without invasion of the bronchus by the growth. In a few instances the paroxysm is brought to an end by expectoration of a small plug of viscid sputum.

If the cough is brassy in character it usually implies involvement of the trachea or bronchus.

The cough may be associated with transitory oedema of the face and neck, and distension of the veins. The paroxysms may be associated with sharp stabbing pain in the chest. They frequently cause insomnia. In some cases the bouts of coughing were accompanied by great dyspnoea and cyanosis, the patients becoming very distressed and crying out for more air. The cough may produce retching and vomiting.

Expectoration. Sputum was present in more than half of the cases. The sputum may be mucoid, muco-purulent, purulent, or mixed with blood. Where bronchiectasis supervenes the sputum is large in quantity and foetid in character. If the tumour is intrabronchial sputum occurs comparatively early. Many observers have reported that streaks of growth and cellular debris may be found in the sputum. These things have not been noted in this series, but I cannot definitely state in how many cases they have been especially looked for.

Haemoptysis. Of these cases with sputum, over 70 per cent. had haemoptysis, although this constituted only 36 per cent. of the total number of cases. The term haemoptysis is used to include all degrees. Thus there may be merely a few streaks of blood in the sputum ; or the blood may be intimately mixed with the sputum, producing the classical 'red currant jelly' appearance; or there may be pure blood either in small quantities frequently repeated or as a large brisk haemoptysis.

Pain. Pain is undoubtedly an important symptom of carcinoma of the lung. Apart from cough it was the most frequent symptom, occurring in 64 per cent. of the cases and being the very first sign in over 20 per cent. of the cases. In many of these latter cases the pain preceded the subsequent symptoms by several months. Pain is often the most prominent of all the symptoms, and may in fact be the only symptom.

Character of the pain. The pain may be of all grades of intensity, slight, severe, or unbearable. It is often described as gnawing in character, but may be sharp or stabbing like neuralgia. In one case there were attacks of 'sharp gnawing pain across the costal margin which doubled me up'. The pain may be 'gripping' or dragging', 'as if my inside was being dragged out'. There may be a feeling of constriction 'like a collar round my neck' or a 'dull gnawing pain in the stomach which passes round to the small of my back till it feels like a tight constricting band which fixes me'. The pain may, on the other hand, be identical with that which occurs in pleural involvement from any cause. In some cases there is no real pain but a feeling of pressure or of suffocation.

Site of the pain. The pain is usually situated in the chest, but may occur in the neck, the back, the loins, the abdomen, down the arms, and even in the legs, simulating sciatica.

Cause of the pain. Pain may be due to a variety of causes, the most common of these being (*a*) involvement of the pleura with or without metastases; (*b*) secondary growth in the vertebrae pressing upon the cord and nerve roots. This latter is responsible for the most excruciating pain and for the pains of constricting or girdle-like character.

Other causes are:

(*c*) invasion of intercostal nerves by metastases in the ribs and pleura.

(*d*) involvement of nerve plexuses (e.g. brachial or lumbo-sacral) by adjacent secondary deposits.

(*e*) pericardial involvement.

(*f*) thrombosis of large vessels.

Wasting. Wasting is an important sign occurring in over 50 per cent. of the cases. It usually occurs during the course of the disease, but may be early or late. In the late stages it is often of great severity. It may be associated with other signs of cachexia such as anorexia, malaise, weakness, sallow or 'café-au-lait' complexion.

Dyspnoea. Dyspnoea occurred in more than half the cases. It is usually a late symptom unless due to a large pleural effusion which may occur at any

stage in the disease. It may occur in all grades of severity, from slight dyspnoea on exertion to marked orthopnoea. Apart from pleural effusion, dyspnoea may be due to direct involvement of a large portion of lung by growth, to occlusion of a large bronchus with resulting diminished air entry, or to associated bronchitis, broncho-pneumonia, bronchiectasis, collapse, &c. The dyspnoea may occur in paroxysms often resembling asthma. These paroxysms have been ascribed to obstructing plugs of mucus, or to vagal involvement. They may be produced by attempting to lie in certain positions, more especially on the same side as the neoplasm. Dyspnoea may occur only during the paroxysms of coughing. The dyspnoea may be associated with inspiratory stridor, due to involvement of the mediastinum and pressure of the growth on the trachea.

Pyrexia. Fever occurred in no less than 54 out of 139 cases. Any variety of pyrexia may occur, as for example continuous, remittent, or intermittent. There may be only a rise of one degree, or there may be a hectic swinging temperature associated with chills and night sweats, the latter occurring in 34 of the series. The temperature usually rises in the evening and falls in the morning, often resembling the temperature chart of a phthisical patient. The pyrexia is usually due to the associated bronchitis, bronchiectasis, and broncho-pneumonia, but many cases showing these pulmonary complications at autopsy appear to have little or no pyrexia during life.

Tachycardia. A rapid pulse is often associated with pyrexia, as one would expect. In 26 cases, however, there was a rapid pulse of 100 or more associated with normal or subnormal temperature. This is probably due to the presence of toxaemia, although involvement of the vagus has been suggested.

Metastases discovered on clinical examination. Metastases were noted in life in about a quarter of the cases. They include secondary deposits in the glands (usually supraclavicular, cervical, axillary glands), in the subcutaneous tissue, in the vertebral column, and in the brain. They may occur at any stage in the course of the disease and in some cases constituted the first sign. I have not included in this group those cases where the primary source was undiscovered in life. The latter are discussed in detail in the section dealing with differential diagnosis.

Cyanosis. Slight degrees of cyanosis are explicable by the associated pulmonary complications. Intense cyanosis is more often due to congestion of veins owing to pressure effects and is then of much significance.

Dilated veins. Although occurring in only about 20 per cent. of the cases, the presence of dilated veins is of the greatest importance as definitely pointing to some obstruction in the mediastinum. The dilated veins may occur in the head and neck, and upper extremities, over the thorax or over the abdomen. The dilatation may only be visible on coughing or stooping.

Oedema. Oedema occurred in about a fifth of the cases and was often associated with dilated veins and cyanosis. It is usually a late sign, but in a few cases was the initial manifestation.

Oedema of the neck and upper extremities when present is very char-

acteristic of carcinoma of the lung, and indicates invasion of the mediastinum. It is due to venous obstruction, produced either by pressure of the growth or by thrombosis, which may or may not be associated with infiltration of the veins by growth.

Oedema of the head and neck may be unilateral, the right side being more frequently involved than the left.

The oedema may be transitory or constant. Thus it may only occur on exertion, or on stooping, or on coughing. In some of the cases the oedema, after persisting for some time, gradually decreased in amount or even disappeared altogether.

Oedema of the neck may be associated with a choking feeling and most intense discomfort.

Other pressure effects. Oedema, dilated veins, and cyanosis have already been discussed. Laryngeal paralysis occurred in no less than 24 out of 139 cases. Dysphagia occurred in 15 of the cases. It is usually a late symptom, but in one case was the first thing noticed by the patient. Vomiting may be due to pressure on the oesophagus, or to secondary deposits invading the stomach. It is, however, more commonly the result of severe paroxysms of coughing.

Pressure on the aortic arch may produce unequal pulses, thus resembling aneurysm.

Inequality of the pupils may be produced by pressure on the aortic arch or by pressure or destruction of the cervical sympathetic.

By involvement of the sympathetic it is said that the characteristic signs of ptosis, narrow palpebral fissure, and retraction of the eyeball may be produced, but these signs were not observed in this series of cases, nor have I personally observed it with carcinoma of the lung.

Headache, vertigo, and inability to stoop may be ascribed to pressure on the superior vena cava and congestion of the brain.

Pressure or involvement of the vagus is said to be responsible for paroxysmal dyspnoea, paroxysmal cough, vomiting, and tachycardia. In most cases the explanation of these symptoms is more obvious on other grounds.

Clubbing of the fingers. Clubbing did not appear to be a conspicuous feature of the disease, its presence being recorded in only nine cases. The majority of these cases showed clubbing of minor degree, but in one case there was exceptionally well-marked hypertrophic pulmonary osteoarthropathy of hands, forearms, feet, and legs (confirmed by radiological examination). It is perhaps possible that minor degrees of clubbing escaped being recorded, as I do not consider clubbing of fingers in carcinoma of the lung to be as rare as these figures indicate.

Physical Signs in the Chest.

The physical signs vary enormously, depending upon the site of origin of the growth, the stage at which examination is made, and the numerous complications. In a characteristic early case, commencing for example in the hilum

of the right lung, the signs may be: dullness to the right of the sternum for an inch or so between, say, the second or fourth ribs and perhaps including part of the manubrium sterni; there is often a normal area between this dull area and the clavicle; over the dull area, the breath sounds are often bronchial, and the tactile vocal fremitus and vocal resonance may be increased; the breath sounds, however, may be greatly diminished, and tactile vocal fremitus and vocal resonance diminished or absent. This is usually associated with blockage of the lumen of a bronchus; for a similar reason the breath sounds at the base of the affected lung may be diminished, and this is often the only sign in an early case.

Where the growth has spread from a bronchus to invade the lower lobe the physical signs described above may be found only at one base.

Adventitious sounds are usually absent in the early stages, but occur later with the complications.

Breath sounds are occasionally stridulous.

During the course of the disease there nearly always appear the physical signs of the common complications, namely bronchitis, broncho-pneumonia, collapse, pleural effusion, &c.

The position of the apex beat is variable and does not appear to be of great help in diagnosis.

Accessory Methods of Examination.

As this series of cases is taken from 1907 to 1925 it gives no opportunity for appraising the value of such modern methods as lipiodol injections, bronchoscopy, and thoracoscopy. I am, however, able to draw some deductions from the results of radiological examination, the character of pleural effusions, and the nature of the blood count.

The Value of Radiological Examination in Diagnosis.

In this series of 139 cases, 52 underwent radiographic examination of the thorax. Of these only 29 were definitely diagnosed radiographically as intrathoracic neoplasm—that is, 56 per cent. In 4 cases the radiologist made the diagnosis of aneurysm, and in 3 cases the radiologist was unable to decide between aneurysm and neoplasm. In the remaining cases the diagnosis was that of the complication instead of the primary condition, or in some cases was insufficiently definite to be of deciding value. Examples of this group of radiological diagnoses are: 'consolidation', 'fluid', 'opacities', 'indefinite shadows', 'patchy consolidation and abscesses', 'chronic infection'.

It would appear from this brief review that the radiologist tends to fall into the same errors as the clinician, and especially is this the case in the differential diagnosis of aneurysm and growth. When the growth is closely adherent to the arch of the aorta, the presence of a pulsating swelling in this situation may offer great difficulties in diagnosis.

In deprecation of the undue stress that is sometimes laid on radiological

examination, it must be admitted that a large proportion of these cases correctly diagnosed radiographically were also obvious clinically.

It is of interest to note that radiographic examination of some of these cases was carried out as early as 1907.

Pleural Effusions.

Pleural effusions were detected in life in 30 out of 139 cases—that is, 22 per cent.

The majority of these, namely 13, were clear serous effusions, 9 were blood-stained, 5 were purulent (empyemata), and 3 were turbid or opalescent.

Of the empyemata 2 were sterile and 3 showed pneumococci.

Of the 13 serous effusions, the majority, namely 8, showed a marked excess of small lymphocytes, with endothelial cells either absent or very few in number. The remaining 5 cases gave the following differential cell counts.

Name.	Small Lymphocytes.	Polymorphonuclear Cells.	Endothelial Cells.
	%	%	%
Poulter	12	5	83
Newson	62	24	14
Manicom	46	47	7
Benzile	No figure given—majority endothelial cells.		
King	The three types of cells present but too fragmentary to count.		

It is thus seen that in only two cases did the endothelial cells preponderate. The absence of an excess of endothelial cells in a pleural effusion is by no means evidence against neoplasm of the lung.

In all 13 cases no organisms were found in the films made from deposits of the effusions, and the cultures were sterile. It is thus seen that, in the majority of clear effusions, cytological examination of the fluid and bacteriological examination of the films and cultures do not enable one to differentiate malignant effusions from idiopathic or tubercular effusions.

No less than 30 per cent. of the effusions were sanguinous. Sanguinous effusions are very suggestive of carcinoma of the lung, but may occur with tubercular effusions. The presence of blood is only of significance in the first paracentesis, as a sanguinous effusion on a second occasion may be the result of trauma.

The rapid and repeated recurrence of a pleural effusion after paracentesis is very suggestive of malignant origin.

One case showed a marked alteration of the cytology of the pleural fluid on subsequent paracentesis. The first paracentesis was performed three months after the onset and two months before death, and showed 95 per cent. small lymphocytes. A second paracentesis made a week later showed 83 per cent. endothelial cells and only 12 per cent. small lymphocytes.

In some cases the pleural effusion is terminal. At autopsy there were 39 cases of pleural effusion of which 20 were clear, 10 sanguinous, 9 purulent. These figures include the clinical statistics already given.

Blood Count in Carcinoma of the Lung.

This was only carried out in 17 cases. The red cell count does not appear to be of any importance, it being normal or showing secondary anaemia of moderate degree.

The white cell count, however, is of great interest, a leucocytosis being present in 14 cases—that is, over 80 per cent. of those examined. Of these cases 8 had a leucocyte count between ten and twenty thousand, and 6 between twenty and thirty thousand. In all these cases there was an excess of polymorphonuclear cells, usually 80 to 90 per cent. of the total white cells.

The leucocytosis was probably due to the associated purulent bronchitis, bronchiectasis, and broncho-pneumonia, which were present in all these cases. Since these complications occur in most cases of carcinoma of the lung, leucocytosis is probably a very common feature at some stage of the disease.

Leucocytosis would therefore be of no value in differentiating from unresolved pneumonia or bronchiectasis, but might be of use in differentiating from an aneurysm unassociated with lung complications.

Diagnosis and differential diagnosis. By comparing ante-mortem diagnosis with post-mortem findings in this series of 139 cases, I have ascertained the proportion of cases correctly diagnosed and the types of error. In a further detailed consideration, I have endeavoured to show in which directions improvement of diagnosis might be sought and how common errors might be avoided.

I have classified the cases into four main groups:

(*a*) Correctly diagnosed in life as carcinoma of the lung.

(*b*) Incorrectly diagnosed in life as carcinoma of the lung, and found to be some other condition at autopsy.

(*c*) Unsuspected in life, and known to be carcinoma of lung only by autopsy.

(*d*) Incompletely diagnosed, such as pleural effusions, the malignant origin of which was not ascertained in life.

Year.	Total Number of P.-M.s on Cases of Carcinoma of Lung.	(*a*) Correctly diagnosed. %	(*b*) Wrongly thought to be Carcinoma of Lung.	(*c*) Unsuspected in Life.	(*d*) Incompletely diagnosed.
1907	6	3 (50)	1	3	0
1908	10	5 (50)	0	4	1
1909	8	4 (50)	1	4	0
1910	7	3 (43)	0	4	0
1911	5	3 (60)	0	2	0
1912	8	3 (38)	0	4	1
1913	8	5 (63)	2	2	1
1914	5	3 (60)	0	1	1
1915	5	3 (60)	0	2	0
1916	4	3 (75)	1	0	1
1917	3	0 (0)	1	3	0
1918	4	3 (75)	0	0	1
1919	6	2 (33)	0	3	1
1920	8	5 (63)	1	3	0
1921	9	6 (67)	1	3	0
1922	10	5 (50)	1	4	1
1923	11	7 (64)	0	4	0
1924	10	3 (30)	0	7	0
1925	12	7 (58)	0	5	0

73 cases were correctly diagnosed out of a total of 139, namely 53 per cent. This figure compares favourably with that of other observers. One striking feature of this analysis is that there does not appear to be any marked improvement in diagnosis, and in fact the greatest number of errors occurred in 1924. I believe that this finding is contrary to what may be regarded as the general impression or belief of the clinician, and is indeed contrary to what might be expected from an increasing familiarity with the disease and the development of accessory methods of investigation. It will be seen, however, that in many cases the differential diagnosis offered the greatest difficulties.

Errors of Diagnosis. The following groups of erroneous diagnoses indicate in which direction error is most likely to occur. It is an analysis of those cases incorrectly diagnosed in life, and discovered to be carcinoma of the lung only at autopsy (66 cases).

Pulmonary Group (24).

Pleural effusions	8	Bronchiectasis	1
Empyemata	4	Broncho-pneumonia	2
Pyopneumothorax	1	Lobar pneumonia and abscess	1
Phthisis	2	Dry pleurisy	1
Bronchitis	4		

Cerebral Group (13).

Cerebral neoplasm	7	Encephalitis	1
Cerebral abscess	1	Encephalitis lethargica	1
Coma	1	Hemiplegia	1
Meningitis	1		

Spinal Group (5).

Transverse myelitis	2	Caries of spine	1
Paraplegia	1	Lumbago	1

Aneurysm (5).

Miscellaneous (19).

Moribund	4	Gastric ulcer	1
Fatal accidents	3	Carcinoma oesophagus	1
Operation for cholelithiasis	1	Carcinomatosis	1
Operation for gastric ulcer	1	Carcinoma suprarenal	1
Peritonitis	1	Vague—no diagnosis	3
Carcinoma ventriculi	2		

Pulmonary group. It is seen that in the majority of cases the diagnosis was that of a pulmonary complication, the primary carcinoma being undetected.

Of the 8 pleural effusions, 2 were apparently indistinguishable from idiopathic effusions. In the remaining 6 cases, the following features might have suggested neoplasm. Thus:

1. Female, aged 63. Liver enlarged and tender (secondary growth), pain in back (due to secondary growth in lumbar vertebrae), great wasting for eighteen months.

2. Male, aged 45. Pain in side and back extending over a period of six months. Blood-stained effusion.

3. Male, aged 50. Seven weeks face and neck swell on slight exertion, husky voice as vocal cords congested. Small dilated venules over the lower chest.

4. Male, aged 45. Pain over a period of nine months. Rapid re-accumulation of pleural fluid after paracentesis.

5. Male, aged 60. Two months dysphagia and hoarseness.

6. Male, aged 42. Dysphagia. Rapid re-accumulation of fluid after paracentesis. Great wasting: two stone.

The age in all these cases was perhaps suggestive of malignant disease.

In the case of dry pleurisy there was no clue to its malignant origin.

In the case of the empyemata and the one pyopneumothorax there was one important feature, common to all the cases, and contra-indicating an ordinary pneumonic condition. This was the gradual onset of the illness with a history of cough and sputum, with or without pain in the side, extending over several months. Furthermore the patients continued at work until a week or so before the discovery of the empyema. It must be admitted, however, that low grade pneumonias with subsequent empyemata occur in old people with such insidious onset and progress. The differential diagnosis in these cases is very difficult, especially when it is remembered that the empyemata in carcinoma of the lung are usually the result of secondary broncho-pneumonia.

Of the 4 cases of bronchitis, 3 gave some indication of the true nature of the disease.

1. Male, aged 64. Husky voice. Wasting.

2. Male, aged 71. Some wasting. Large haemoptysis three days before death.

3. Male, aged 36. Liver enlarged and tender (metastases).

4. Male, aged 44. Oedema of face and neck.

In the case of bronchiectasis, apart from severe loss of weight (3 stone in eighteen months), there was nothing to indicate carcinoma.

One case of broncho-pneumonia was very vague, but another had oedema of face and neck and dilated veins.

In the case diagnosed as lobar pneumonia and lung abscess both these conditions were found *post mortem*, and clinically there was no indication of their being secondary to a malignant condition.

Both cases of alleged phthisis were apparently diagnosed on insufficient evidence, and the sputum was negative. There was no real indication of carcinoma of the lung, but in one case the pain, extending over a period of four months, was too severe and persistent to support the wrong diagnosis of phthisis.

Although only two of this series were thought to be phthisis, it would appear from the literature that this is not an uncommon error. Lynham (15) points out that in the sanatorium post-mortem rooms there are encountered examples of new growth associated with tuberculosis and unsuspected during the patient's lifetime. Historically it is of interest to note that Bayle (16) in 1810 described carcinoma of the lung as 'phtisie cancereuse', one of his six varieties of phthisis.

The differentiation of carcinoma of the lung from phthisis is not always

easy. Wasting, cough, sputum, dyspnoea, haemoptysis, and even night sweats may be prominent in both diseases. Pain is much more significant of carcinoma of the lung, especially when very severe, but pleuritic pain not infrequently occurs with tuberculosis. Pressure signs, especially dilated veins and oedema of head and neck and upper extremities, almost certainly indicate neoplasm. Secondary glands are diagnostic. Pyrexia is frequent in tuberculosis, but often occurs in neoplasm with secondary infection. Tuberculosis patients are usually under 40, while those with neoplasm are more commonly over 40. Neoplasm affects the upper lobe more commonly than the lower (41 upper lobe, 29 lower lobe, 67 indeterminate), but not nearly to the same extent as tuberculosis. The presence of the tubercle bacillus in the sputum proves pulmonary tuberculosis but does not necessarily exclude a co-existing carcinoma of the lung.

To conclude a consideration of the pulmonary group as a whole, it would appear from a review of the cases that about 50 per cent. of the errors might have been avoided if greater significance had been attached to certain features that were characteristic of carcinoma of the lung.

Cerebral group. This constitutes a very large group, and the differentiation from primary cerebral conditions is therefore of great importance. In this group of 13, the cerebral symptoms were due in 11 cases to a cerebral metastasis, the remaining two being merely coincident conditions. In the whole series of 139 cases, cerebral metastases occurred in 19. Therefore in 11 out of 19 cases (that is, 58 per cent.) where secondary growth occurred in the brain, the primary pulmonary focus was not detected. The explanation of this large source of error is twofold :

(*a*) The cerebral metastasis may occur very early with a latent localized condition in the lung, and (*b*) the cerebral manifestations are often sufficiently dramatic to dominate the clinical picture. To such an extent do these factors operate that some of these cases actually had cerebral decompression performed, the absence of the primary focus being undetected.

In a review of this group it would appear that less than half of the cases gave a clue to the real diagnosis. Wasting was a definite feature in four cases and might have aroused suspicion as to the primary origin of the cerebral tumour. Other suggestive symptoms and signs were dyspnoea on exertion, bronchitis, haemoptysis, hoarseness, offensive breath (bronchiectasis), and leucocytosis.

It should be realized, however, that many of the cases were admitted semi-comatose or suffering from convulsions or moribund, without any pulmonary history, and in such circumstances it was often not possible or perhaps inadvisable to attempt a complete examination of the chest. It does seem, however, that fewer cases will escape diagnosis when one appreciates the potential latency of carcinoma of the lung, and the possibility of its initial manifestations being those of a cerebral metastasis.

Spinal group. The remarks of the previous section on the cerebral group apply with equal force here. In most cases the spinal symptoms are due to secondary growths in the vertebral column pressing upon the spinal cord. It is

rare for a metastasis to occur in the cord itself. This happened in only one of our cases, although secondary growth in the vertebrae occurred in no less than 29 cases. Of these 29 cases, however, paraplegic symptoms were present in only seven.

Aneurysm. The differential diagnosis of intrathoracic neoplasm from aortic aneurysm is a classical problem which may offer considerable difficulty.

Both diseases occur much more frequently in men than women, pain is a common and prominent feature in both cases, and may be unbearable both in aneurysm and neoplasm, being in such circumstances due to erosion of vertebrae or metastasis in the vertebral column respectively. Hoarseness occurs not infrequently in both conditions, although perhaps more commonly in aneurysm. Dyspnoea and cough occurs with both.

Brassy cough, unequal pupils, unequal pulses, tracheal tug, and expansile pulsation are very suggestive of aneurysm, but all of them may occur in carcinoma of the lung. For example, the unequal pulses are due to pressure of the growth on the aorta causing a partial constriction, the expansile pulsation may be due to adherence of the growth to the aorta, and further adhesions to the trachea or large bronchi may produce the phenomena of tracheal tugging.

A diastolic shock, and aortic systolic thrill and murmur, and a loud or ringing aortic second sound, and possibly an aortic diastolic murmur, are of course all recognized characteristics of aneurysm. A systolic murmur may be heard over a growth. A positive Wassermann reaction is very suggestive of aneurysm, but may coexist with neoplasm of the lung. Aneurysm is most common between the ages of 35 and 45, whereas neoplasm is most common between 45 and 60.

Haemoptysis, dilated veins, and oedema are very characteristic of intrathoracic neoplasm, but may nevertheless occur with aneurysm. Haemoptysis in aneurysm is most often of large amount and fatal, but small recurring haemoptyses may occur for some months.

Wasting, cachexia, metastases, pyrexia, pleural effusion, and sputum are all strongly in favour of carcinoma of the lung.

The clinical picture may be complicated by pressure of an aneurysm on a bronchus with resulting constriction, diminished air entry, collapse, bronchiectasis, and bronchitis. In these cases the lung signs and symptoms may be quite prominent, making diagnosis most difficult. The left bronchus is usually affected and in most cases the lower lobe.

A leucocytosis is strongly in favour of carcinoma of the lung, unless pulmonary complications have occurred with an aneurysm. Radiographic examination may be of no help when the growth is adherent to the aorta.

In our five mistaken cases, wasting occurred in four and might have aroused suspicion. Anaemia, foul breath, and dilated veins were other signs suggestive of the correct diagnosis. In one case the clinical evidence was apparently overweighed by incorrect radiographical diagnosis. In two of the cases there were co-existing aneurysms as well as carcinoma of the lung.

Miscellaneous group of errors. In the two cases operated on for chole-

lithiasis and gastric ulcer respectively, these diagnoses were confirmed at operation, but the patient died shortly after, and carcinoma of the lung was found at autopsy. Thus the lung condition was latent. This was also true of the three accident cases. It is therefore apparent that carcinoma of the lung may be present without manifesting itself in any gross manner. The peritonitis case was of interest in that it followed a few weeks after what was believed to be an attack of pneumonia. Pneumococci were cultivated from the pus found at operation. The peritonitis was secondary to a broncho-pneumonia that had supervened on the carcinoma of the lung.

Dyspepsia may occur in carcinoma of the lung. When combined with cachexia, carcinoma of the stomach may be suspected. In one case, however, the stomach was invaded by growth probably by direct spread from the gastro-coronary glands. Apparently gastric ulcer may be simulated.

The mistaken diagnosis of carcinoma of the oesophagus draws attention to the occurrence of dysphagia in carcinoma of the lung. Dysphagia may occur quite early, but it is usually a late symptom. The oesophagus may be directly invaded by growth, or the growth may press on the oesophagus from outside, or the oesophagus may be kinked and stretched over the growth. Malignant glands may similarly affect the oesophagus. Diagnosis may be difficult, as primary carcinoma of the oesophagus sometimes penetrates into the lungs or bronchi.

The case diagnosed as carcinoma of the suprarenals was of interest in that extensive secondaries had destroyed the suprarenals and there was general pigmentation of the skin and also of the buccal mucous membrane.

The group just considered is a fairly large group and illustrates the various pitfalls in the diagnosis, but at the same time it does not appear from the study of the cases that many of the errors in this group could have been avoided.

Incorrectly diagnosed in life as carcinoma of the lung. There were nine cases in which the post-mortem findings showed, contrary to expectations, conditions other than carcinoma of the lung.

Lymphogranulomata	4
Carcinoma thyroid	1
Carcinoma thymus	1
Lymphosarcoma thymus	1
Fibrosarcoma mediastinum	1
Carcinoma nasal turbinate bones . . .	1

In most of these cases the thorax contained metastases or direct extension of growth, and diagnosis was difficult or impossible. Biopsy of a gland in the lymphogranulomata might have assisted diagnosis, although some of them showed atypical sections at autopsy.

In the case of the carcinoma of the nasal turbinate bones the primary was very insignificant compared with the massive intrathoracic secondaries.

Neoplasm of the thymus simulates carcinoma of the lung very closely, clinical diagnosis often being impossible. Considered merely from a numerical point of view, the clinical differential diagnosis is of no great importance.

It seems apparent from this study that the erroneous supposition that a case is carcinoma of the lung only accounts for a small proportion of the total errors of diagnosis.

Treatment.

No drug appears to have any specific effect. In this series of cases there was no attempt to remove the growth surgically. A study of the morbid anatomy of carcinoma of the lung, and the frequency of local and general metastases, would not appear to justify optimistic expectations of good results from this method of treatment, although it must be admitted that some surgeons claim a measure of success.

Radiation was tried in nine cases with varying results. In seven cases, however, there was subjective improvement, especially as regards alleviation of pain. In one case the physical signs showed a decrease in the size of the tumour, and in another case a superficial secondary deposit was made to disappear for several months. Radiation may have no apparent effect or may even cause an exacerbation of symptoms.

In the majority of these cases the condition was well advanced before the radiation treatment commenced. From these few cases it has not been possible to conclude that X-ray therapy prolongs life, but the frequent amelioration of symptoms justifies its use.

Radium treatment is now being tried at the London Hospital, but it is too early to estimate its value.

The alleged Increase in Primary Carcinoma of the Lung.

An apparent increase in the incidence of primary carcinoma of the lung has been reported on the Continent (Germany and Switzerland in particular), in America, and in this country.

The more important of these investigations are considered in this paper, and a further contribution to the subject under discussion is made by a complete analysis of the clinical and post-mortem records of the London Hospital from the year 1907 to 1925. In this series there were 332 clinical cases and 139 post-mortem examinations.

Moses Barron (2) investigated the records of the Department of Pathology at the University of Minnesota.

Year.	Total Autopsies.	Carcinoma of Lung.	Percentages.
1899–1911	1333	0	—
1912–1918	2026	4	0·2
1919–1921	1003	9	0·9

This series is not a large one. There were no cases of carcinoma of lung prior to 1912, and the increased incidence was most marked from 1918–1919.

To compare with his own figures Barron quoted some other observers. Thus:

Year.	Name.	Percentage Carcinoma of Lung to Total Carcinomata.
1878	Reinhard	0·057
1895	Fuchs	0·067
1894	Pässler	0·083
1894	Wolf	0·223
1907	Oerstrom	0·310
1916	Briese	0·460
1919–1921	Barron	0·900

These collected statistics indicate a gradual increase extending over many years.

B. M. Fried (17) points out that in the Hellenic Hospital, New York City, from 1907–19 there were only five primary lung tumours, but in the next twenty months there were seven cases.

In the Peter Bent Brigham Hospital from 1913–21 there were no cases of primary malignant disease of the lungs, but from 1921 to 1924 there were five cases.

Moise (18), writing in 1923, states that, according to composite statistics, carcinoma of the lung prior to 1917 constituted about 1 per cent. of all carcinomata, but in the last three years at the New Haven Hospital, Connecticut, carcinomata of the lung constituted 17 per cent. of all carcinomata. This latter figure appears to be exceedingly high compared with those of other observers, but a marked increase in recent years seems very definite.

Staehelin (19) gives the following statistics from the Basel Pathological Institute:

Year.	Total Autopsies.	Carcinoma of Lung.	Percentage Carcinoma of Lung to Total Autopsies.
1900–1911	7372	10	0·20
1912–1914	2092	11	0·50
1915–1923	6546	41	0·63
1924	749	5	0·67

He also submits some data, calculated on a slightly different basis, from the Bürgerspital:

Year.	Total Carcinomata.	Carcinoma of Lung.	Percentage of Lung to Total Carcinomata.
1900–1911	566	12	2·1
1912–1914	218	11	5·0
1915–1923	755	38	5·0
1924	81	4	4·9

From both series of figures it would appear that the increase occurred in the period 1912–14. The Basel data show a gradual increase after this, but the Bürgerspital figures remain fairly constant.

In contrast to this increase in carcinoma of the lung, Staehelin (19) quotes Tessen's conclusion that in Basel there is apparently no increase in deaths from malignant neoplasms of all parts of the body (1870 to 1919).

Kikuth (3) studied the post-mortem material at the Effendorf Hospital in Hamburg for 35 years and gives the following figures :

From 1889–1900, 10 cases carcinoma of lung.
„ 1900–1911, 90 „ „ „
„ 1912–1923, 146 „ „ „

In 1923 there were no less than 22 cases of carcinoma of the lung, which number constituted 9·4 per cent. of the total carcinomata.

Kikuth (3) quotes Seyfarth as finding carcinoma of the lung to be 15·5 per cent. of all carcinomata occurring in Leipzig in the first half of the year 1924.

He also quotes Lubarsch's figures for the whole of Germany 1920–21—carcinoma of lung constituting 5·4 per cent. of all carcinomata.

Kikuth concludes that there has been a definite increased incidence of carcinoma of the lung in recent years.

Sonnenfeld (20) has investigated the post-mortem records in a Berlin hospital.

Year.	Total Carcinomata.	Carcinoma of Lung.	Percentage Carcinoma of Lung to Total Carcinomata.
1912	34	1	2·9
1913	48	1	2·0
1914	56	1	1·8
1915	77	2	2·6
1916	69	1	1·4
1917	71	3	4·2
1918	67	5	7·5
1919	85	3	3·5
1920	77	4	5·2
1921	84	6	7·1
1922	89	7	7·8
1923	98	9	9·2
1924	110	11	10·0
1925	180	16	8·9

This series indicates a marked increase in the number of cases of carcinoma of the lung, the increase commencing about the year 1917.

Berblinger in Jena, where the majority of deaths are followed by autopsies, found a definite increase in the incidence of carcinoma of the lung.

Year.	Percentage Carcinoma of Lung to Total Carcinomata.
1910–1914	2·2
1920–1924	8·3

The increase appears to have occurred in recent years. Duguid (6), from a study of intrathoracic tumours in Manchester, also finds an appreciable increase in their incidence.

Year.	Post-mortems.	Malignant Intrathoracic Neoplasms.	Percentage.
1871–1885	2107	5	0·24
1886–1890	1014	16	1·58
1891–1895	1175	15	1·28
1896–1900	991	12	1·21
1901–1905	1083	26	2·40
1906–1910	898	12	1·34
1911–1915	1141	27	2·37
1916–1920	910	22	2·42
1921–1925	1126	29	2·57

As evidence of the apparent rarity of primary malignant disease of the lung 25 years ago, Rolleston and Trevor (21) in 1903 found in a series of 3,983 autopsies only 8 cases of intrathoracic malignant disease.

TABLE I.

London Hospital Statistics—Post-mortem Study.

Year.	A. Autopsies.	B. Carcinoma of Lung.	Percentage $\frac{B}{A}$.
1907	1182	6	0·51
1908	1289	10	0·78
1909	1288	8	0·62
1910	1208	7	0·58
1911	1265	5	0·40
1912	905	8	0·88
1913	878	8	0·91
1914	784	5	0·64
1915	719	5	0·69
1916	653	4	0·61
1917	581	3	0·52
1918	615	4	0·65
1919	645	6	0·93
1920	750	8	1·07
1921	598	9	1·50
1922	589	10	1·70
1923	604	11	1·82
1924	578	10	1·73
1925	585	12	2·05

In considering these figures it is necessary to point out that the marked decrease in the total number of autopsies is mainly due to failure to secure consent for post-mortem examination. In 1907 autopsies were performed on 91 per cent. of cases dying in hospital; in 1925 such examination was made on only 69 per cent. In addition, the total yearly deaths have fallen from 1,292 in 1907 to 838 in 1925 whereas the total number of patients admitted each year has increased from 13,532 in 1907 to 17,467 in 1925.

The incidence of primary carcinoma of the lung as measured by the percentage of the total autopsies shows a marked increase, it being four times greater in 1925 than in 1907.

The most rapid increase appears to have occurred from 1918 to 1922, although there is also some increase in later years.

In addition to the statistical study based on post-mortem evidence alone, a further analysis has been made, based on both clinical and post-mortem evidence.

TABLE II.

Combined Clinical and Post-mortem Study—London Hospital.

Year.	A. Total Malignant Neoplasms.	B. Carcinoma of Lung.	Percentage $\frac{B}{A}$.
1907	607	6	1·0
1908	618	13	2·1
1909	753	14	1·9
1910	724	12	1·7
1911	814	15	1·8
1912	708	11	1·6
1913	750	17	2·3
1914	835	13	1·6
1915	878	17	1·9
1916	663	14	2·1
1917	866	9	1·0
1918	666	17	2·6
1919	753	18	2·4
1920	744	20	2·7
1921	682	24	3·5
1922	720	22	3·1
1923	777	31	4·0
1924	744	28	3·8
1925	830	31	3·7

This has enabled us to include a much larger number of cases (332). It is probable that the error due to possible clinical fallacies does not detract greatly from the value of the data for the following reasons: Only those cases that were clinically certain to be carcinomata of the lung have been included, and the same critical method of review has been practised in similar manner for all years. Many of the cases had obvious clinical secondaries, and in some a gland was excised and histological examination carried out. In others the X-ray examination was very definite and in keeping with the physical signs and clinical diagnosis. An analysis of mistaken diagnoses as shown by post-mortem findings reveals the fact that very few of the cases said to be carcinoma of the lung clinically are found to be some other condition at autopsy, the majority of mistakes being those of omission, i. e. failure to recognize the condition. Such mistakes of omission would appear to affect the figures for each year proportionally, occurring almost as frequently in later years as in the earlier periods. Apart from these considerations, it must be remembered that post-mortem examinations were conducted in about half the number of cases included in this second series.

It is of interest to note that the figures thus obtained show a fair correspondence with those based solely on autopsies. They show a definite increase in the incidence of carcinoma of the lung, the increase being most marked from 1918 to 1923. During the last few years (1923–5) carcinoma of the lung constitutes nearly 4 per cent. of the total carcinomata.

Is the Increased Incidence of Primary Carcinoma of the Lung apparent or real?

An apparent increased incidence is agreed to by most observers. Before concluding that this is a real increase one must eliminate alterations in pathological conception and improvements in clinical diagnosis. As has been discussed in the pathological section, there has been an alteration in pathological classification, as a result of which the mediastinal sarcomata are now classified as carcinomata. It is possible that this might affect some statistics, but in actual fact the majority of those who have compiled statistics on the subject have taken cognisance of this fact. Further, the figures of those who use the comprehensive term 'malignant intrathoracic neoplasms' nevertheless manifest an increased incidence of the same order as other observers.

As regards the statistics put forward in this paper, I have already pointed out that Professor Turnbull, Director of the Pathological Institute, has believed in the carcinomatous nature of the 'oat-celled tumour' for many years, and he has been good enough to review the microscopic sections of every case included in this series, that is to say, as far back as 1907.

As regards improvement in diagnosis this would not directly affect the statistics based on post-mortem studies. It might, however, be suggested that the more cases diagnosed as intrathoracic neoplasm in life the greater would be the number for which post-mortems were sought. Even granting this premise, it will be seen from a review of the errors of diagnosis in this series that there has been no appreciable increase in the percentage of cases correctly diagnosed, the greatest number of mistakes occurring as recently as 1924. This observation, although somewhat surprising, is, I believe, due to the fact that clinical history and clinical examination are much more important factors in correct diagnosis than accessory methods, which for the most part are only of a confirmatory nature. At any rate, it is undoubtedly true that improvement in diagnosis cannot explain the increased incidence shown by the series I have reviewed.

It is therefore necessary to conclude that this increased incidence in carcinoma of the lung is a real increase, and furthermore statistics made from the London Hospital records indicate that it is not associated with an increase in the total carcinomata of all parts of the body.

In arriving at this conclusion it is admitted that statistics are open to sources of error, most of which I have, however, endeavoured to eliminate. It might be argued that inoperable carcinomas are sometimes not admitted to hospital, and that an increased interest in neoplasms of the lung has contributed towards the increased admissions to hospital. While not denying the possibilities, I do not consider that these factors have operated to any extent, or that they detract from the value of the statistics.

Aetiology of Carcinoma of the Lung.

The question of the aetiology of carcinoma of the lung has given rise to much discussion. Since the increased incidence in recent years is a real one, it

is pertinent to bear in mind those potential aetiological factors which themselves are known to have an increased incidence. It will be convenient to consider the various theories under separate headings.

Influenza as an aetiological factor. The possible connexion between influenza and carcinoma of the lung can be considered from several points of view. On the statistical side, great stress has been laid on the fact that the increased incidence of carcinoma of the lung as determined by several investigators appears to start from the time of occurrence of the great influenza epidemic of 1918–19. Thus in America the statistics of Barron (2), Fried (17), and Moise (18), all showed an increase from 1918. On the Continent the evidence is conflicting. Berblinger's (22) figures certainly show a marked increase in the years following the influenza epidemic. Sonnenfeld's (20) statistics indicate an increase from 1917, a more marked increase in 1918, and then a further increase from 1921 to 1923, after which year the incidence remains fairly constant. Staehelin (19), however, observes that there was a sharp increase in Basel as early as 1912, that is several years before the influenza epidemic.

Hampeln (23) found that the increased incidence occurred as early as 1900. Ferenczy and Matolcsy (8) also noticed a definite increase prior to 1914, but in addition there was a further increase after 1918.

In this country Duguid's figures for Manchester (1871–1925) show a somewhat irregular increase bearing no very obvious relationship to the influenza epidemic of 1918–19.

The post-mortem statistics of the London Hospital indicate an increase, which is most marked for the period 1919–22, during which time there was a steady rise followed by a further but less regular increase from 1922–25. The combined clinical and pathological statistics warrant similar deductions although the increase appears to commence a little earlier, namely 1918.

It would seem, then, that the majority of investigations support the view that there was at any rate a further increase following upon the influenza epidemic of 1918–19. On the other hand, many statistics show that an increased incidence has occurred prior to and independent of the influenza epidemic. The fact that the increase continued for several years after the influenza epidemic cannot be considered to rule out its aetiological importance, as it is known that irritative factors may not produce results until some time after they have ceased to operate.

It is possible, however, to regard the statistical evidence as mere coincidence, but evidence in favour of a cause and effect view is forthcoming from histological observations. Thus Askanazy (24) suggests that the pathological changes seen in the lung in cases of influenza resemble a precancerous epithelial proliferation. Confirmatory evidence of this view is also brought forward by Myer and Goldzieher (25).

From clinical observations it must be admitted that a previous history of influenza in cases of carcinoma of the lung is not common. Thus Staehelin (19) points out that of his 17 cases that occurred in the post-influenzal period (1918–23) only four gave a history of influenza. In the London Hospital series of 139

cases, 40 had a history of previous lung trouble, of which 11 had pleurisy, 6 pneumonia, 5 influenza, and 18 chronic bronchitis. These figures do not lend support to the theory that influenza or any previous lung trouble can be considered of important aetiological significance. It should be remembered, however, that the routine recording of previous illnesses may be inadvertently omitted, and in such cases the latter are assumed, possibly erronously, not to have occurred. Post-mortem evidence of pre-existing lung trouble is by no means free from fallacies, and the differentiation of old lesions from those complicating carcinoma of the lung may be impossible. Another point of great significance is the apparent onset of carcinoma of the lung as an acute illness resembling influenza. There may be partial recovery, or even apparently complete recovery, for a short period. Are we dealing with an acute inflammatory disease followed by malignant changes, or with cases of carcinoma of lung manifesting themselves by an acute onset, probably due to an acute complication? The latter view is certainly true in many cases, but it may be that both theories are correct. In this series of 139 cases, no less than 20 appeared to commence as influenza, pleurisy, pneumonia, or acute bronchitis. There was partial recovery in 14 cases (with, for example, the persistence of some cough and sputum) and apparent complete temporary recovery in 6 cases.

Irritation by Inhalation.

It has been recognized for some time that certain mining operations produce a chronic inflammation known by the term pneumonoconiosis. Pure carbon dust appears to do no great harm, but stone dust produces diffuse fibrosis, pleural thickening, and scattered fibrous nodules, often of large size. Bronchiectasis may supervene. The commonest complication of silicosis of the lung observed in the South African mines (26) is tuberculosis. Carcinoma of the lung is a rare complication only occurring together with silicosis in 2 cases during the years 1924 to 1926. Apart from silicosis it occurred in 5 cases during that period.

In Schneeberg, Saxony, however, malignant changes have been known to occur on a large scale for many years, whereas tuberculosis is comparatively rare. Arnstein (27) reports that one-third of all the miners in the Schneeberg district admitted to the hospital in the years 1907–11 were admitted with a diagnosis of pulmonary cancer. Recently 154 cases were investigated by the Saxon Cancer Committee. The majority had suffered from cough and blood-stained sputum for many years, the symptoms probably being due to silicosis. Carcinoma of the lung was diagnosed in 21 cases, and in 13 who died the autopsy confirmed the diagnosis. Of all the cases investigated only a few gave evidence of tuberculosis, and there was nothing to indicate a specially high incidence of tuberculosis among mine workers. The high incidence of carcinoma of the lung among the miners was in marked contrast with the rest of the population, in which carcinoma of the lung was a comparatively rare occurrence. Why miners in Saxony have such a high incidence of malignant change in the lung, whereas those of South

Africa are subject only to tuberculosis, is a problem of the greatest interest. Silica is the main irritant in South African mines, whereas in Saxony cobalt, bismuth, and arsenic are concerned, and in addition the atmosphere is said to be radioactive. The abundant growth of fungi in the Schneeberg mines is a further possible aetiological factor which has not yet been eliminated. It may be that the arsenic of the mines is the important carcinogenic factor, as Jonathan Hutchinson (27*a*) in 1888 drew attention to carcinoma of the skin following prolonged administration of even small doses of arsenic by mouth.

Apart from the mining industry, it appears apposite to consider occupations which involve a dusty atmosphere containing fine particles, such as potteries, metal works, building processes, tobacco works, and other dusty occupations. Investigation of the occupations of the London Hospital series fails to attach an undue proportion of blame to any particular occupation. As these cases extend many years back, there is a possible source of fallacy. Thus in a case I saw recently a man described himself as a jeweller, and might have been labelled such. On further inquiry I elicited the fact that he worked with a machine that bevelled down the gold in a sand-paper process that resulted in a dusty atmosphere heavily laden with minute particles. It is, therefore, of importance to inquire into the details of occupation, and this is now being done, but collective statistics on this point are at present rather scanty.

The statistics, however, did show an apparent excess of outdoor workers. This would at first sight appear to contradict the suggestion of the last paragraph, but rather does it bring into consideration such possible aetiological factors as road dust, tarring of the road, and the fumes of motor exhausts. The proportion of males to females in this series was 4 to 1, whereas for all cases in the hospital males and females were admitted in about equal proportions. Of the males in this series, 60 per cent. were outdoor workers as compared with 39 per cent. in a series of 1,000 consecutive cases of all illnesses, or as compared with 25 per cent. given in a list from the Department of Public Health. Duguid (6) also found a greater proportion of outdoor workers, and in his cases transport workers were particularly liable. Seyfarth (28) found that labourers and hard workers were especially affected, but Kikuth's (3) experience was not in agreement with this observation.

Among the possible sources of inhaled irritants, tar is conspicuous for its known potentialities. Both clinically and experimentally the fact that cancer of the skin may follow upon chronic irritation with tar has been long recognized and accepted. How far this can explain the increased incidence of carcinoma of the lung is as yet a matter of conjecture. On the experimental side Kimosa (29) produced lung cancer in rabbits and guinea-pigs by insufflating tar through a tracheotomy wound. Möller (30) painted the backs of rats with tar and observed in six of his animals, not cancer of the skin as expected, but cancer of the lungs. Clinically there is as yet no direct correlation of tar with carcinoma of the lung. It is true that there has been an enormous increase in the practice of tarring of the roads, but there is not sufficient evidence to justify correlating this

fact with the increased incidence of carcinoma of the lung. The fact that carcinoma of the lung is very rare in places like Hong-Kong and Singapore, where the roads are not tarred, is possibly suggestive. The obtaining of statistics to investigate any co-relationship between the extent of tarring of the roads and the incidence of carcinoma of the lung in different districts and different countries offers many difficulties; but when one considers the widespread practice of tarring (half a million tons of tar are used annually in this country), the known potentialities of tar as an irritant factor, and the undue proportion of males and outdoor workers, it is obvious that here lies an urgent problem that demands scientific solution.

As regards the less specific irritants met with in the streets, and the various combustion products of motor engines, there is no available scientific evidence.

As regards the general theory of inhaled particles, Adler (9) has suggested that as the right bronchus is shorter, wider, and more vertical than the left, it would be more prone to the penetration of foreign bodies and irritating particles, and one would therefore expect the right lung to be more frequently affected than the left. Barron (2) finds this to be the case, but the majority of observers (Fishberg (13), Adler (9), Kikuth (3), Duguid (6)), find no disproportion between the right and left lungs. In this series of 139 cases I find the right lung was involved in 69, and the left in 70. As we are considering minute particles freely disseminated, I do not consider this point to be of much significance.

The latency of an assumed pre-cancerous condition was a factor of interest brought out by the Saxony investigation, 2 out of 21 miners developing carcinoma of the lung several years after ceasing to work in the mines.

Tuberculosis and Cancer of the Lung.

The possible connexion between tuberculosis and cancer of the lung is much disputed. Morris and Landis (31) report that in 662 autopsies at the Phipps Institute there was no instance of tuberculosis. Kikuth (3) does not find any evidence that tuberculosis is an aetiological factor in cancer of the lung, although there was some evidence of tuberculosis in 22 out of 246 cases. In Fried's (17) cases none showed evidence of tuberculosis.

On the other hand, Fried (17) quotes Ewing's opinion that 'the chief aetiological factor in carcinoma of the lung is tuberculosis'. Ewing drew an analogy with carcinoma of lung supervening on the healed scar of lupus vulgaris, but the effect of X-ray treatment complicates this issue. Fox (32) in 1891, in a review of 112 cases, found there was evidence of tuberculosis in only three. Wolf (33) in 1891 reported evidence of tuberculosis in 13 out of 31 cases of malignant disease of the lung, but Shaw (34) considers the evidence unconvincing. Fowler and Godlee (35) in 1898 found tuberculosis in 2 out of 30 cases of malignant disease. Marchesani (36) found tuberculosis in 7 out of 26 cases. Letuelle (37) in 1920 reported two cases of primary cancer of the lung developing in the vicinity of tuberculosis in active evolution. Of Adler's (9) series of 372

cases, 19 had evidence of tuberculosis. Of Ferenczy and Matolcsy's (8) 282 cases, 44 showed healed tuberculosis at apices, or calcareous bronchial glands, or occasionally old cavities. There was only one case of acute tuberculosis.

Cherry (38) in 1925 expressed the view that cancer attacks in later life those who have overcome the attacks of tubercle in early life. He considers that acquired resistance to tuberculosis is the predisposing cause of cancer, that the cells probably react in a different way to the same stimulus, the tubercle bacillus. He points out that the sum of the combined mortality rate for phthisis and cancer has varied very little for thirty years, constituting approximately 20 per cent. of all deaths after the age of 25. His figures indicate that the percentage deaths from cancer are increasing and those from tuberculosis decreasing. The evidence is mainly statistical. In this connexion the observation made in a previous paragraph is of some significance, namely, that pneumonoconiosis in South African mines is associated with much tuberculosis and little carcinoma, whereas in the Schneeberg mines carcinoma is common and tuberculosis rare.

In the London Hospital series of 139 cases, 47 showed some evidence of tubercular infection of the lung. Of these, however, only 6 showed active tubercular lung infection. Seven cases showed healed tuberculous nodules. Thirty showed calcareous glands in or about the hilar region, and in four cases there were mesenteric tuberculous glands. In considering these figures it must be remembered that post-mortem evidence of old tubercular lesions, especially in the form of calcareous glands, is common.

Syphilis and Carcinoma of the Lung.

Syphilis has been suggested somewhat vaguely as one of the aetiological factors in carcinoma of the lung (Schmoller (7)). There is, however, no very convincing evidence in the literature. In the London Hospital series of 139 cases 6 showed evidence of syphilitic lesions. Four showed syphilitic aortitis, of which 2 also had syphilitic fibrosis of the testicle.

The remaining two were of great interest. One had syphilis of the lung, and the other had syphilis of the lung, liver, and kidneys. In both cases the syphilitic and neoplastic changes occurred in the same area of lung, although it is difficult to state on histological grounds that the one arose from the other.

Conclusions on the Aetiology.

It is obvious from the above studies that no one factor will explain the aetiology of carcinoma of the lung or its increased incidence. Many of the aetiological factors might be grouped under the one heading 'irritation', although this must be subdivided into mechanical, chemical, bacteriological, and possibly radiological. It must be admitted that in no one case has the aetiology been conclusively proved, but I consider that there is a considerable amount of suggestive evidence in favour of irritation. The acceptance of irritation as an

important aetiological factor would bring carcinoma of the lung into line with many other forms of cancer. There is no reason to assume that carcinoma of the lung is different in essentials from other carcinomata, and the final solution of its aetiology will probably be forthcoming with that of carcinoma in general. I believe, however, that it offers a fruitful field for investigation, on clinical, pathological, and experimental lines, of the problems of malignancy.

Appendix.

As the limitations of space prevent recording all the cases in this series, I have included in this appendix only those cases which best illustrate some of the main points raised in this paper. The clinical observations are recorded with brevity, but include reference to all the relevant features. The pathological descriptions are restricted to those aspects that explain the symptomatology and physical signs.

With Intracranial Metastases.

1. Male, aged 39. Perfectly well until one month ago, since when he complained of persistent headaches (usually frontal, occasionally occipital), vomiting two or three times a day, giddiness, ataxia, failing vision, diplopia, slight dyspnoea on exertion, and loss of weight.

On examination. Wasting. Papilloedema with flame-shaped haemorrhages in both retinae. Reflexes normal. Babinski negative. Defective sense of passive position in hands and feet. Heart, lungs, and abdomen normal. Wassermann reaction negative. Cerebrospinal fluid normal. X-ray of skull negative. Temperature 98°. Pulse 70. Respirations 24. This case was thought to be primary cerebral tumour.

Post mortem. Nodule of carcinoma $2 \times 1{\cdot}2 \times 1{\cdot}3$ cm. in hilum of right lung close to main bronchus. Nodule of secondary growth 2·5 cm. diameter in right lobe of cerebellum.

2. Male, aged 28. Twelve months ago patient had a slight haemoptysis. A month later he was in bed for five weeks with pleurisy on left side. He then worked again for several months, when twitching of right arm and leg commenced. At about that time he caught cold and developed a troublesome cough. For three weeks he had a hoarse voice. Patient lost 1½ stone in weight.

On examination. Blood-streaked sputum. Stony dullness and diminished breath sounds on left side of chest. Left vocal chord paralysed. Left facial weakness. Inco-ordination left arm. Spastic weakness both legs with brisk reflexes, right greater than left. Babinsky reflex on right and indefinite on left. Temperature 98–99° F. Pulse 100–120. Respirations 26.

Post mortem. Large mass of growth occupying hilum and almost the whole of lower lobe of left lung. Bronchiectasis. Secondary nodules in left optic thalamus, right and left temporal convolutions, left parietal and frontal convolutions, and cerebellum.

Comments. A correct diagnosis was made in life.

3. Male, aged 42. Three months ago squint developed. Two months ago weakness of right arm and leg occurred, and was soon followed by weakness of left face. Shortly afterwards headache, vomiting ensued, and for one month husky voice, cough, sputum, pain in right side and loin, and wasting were complained of.

On examination. Paralysis left external rectus. Paralysis of whole of left side of face. Fundi normal. Lateral nystagmus to right and left. Unsteady spastic gait. Spastic paralysis and some impaired sensation right leg. Signs of bronchitis developed in hospital. Temperature 98° F. (later irregular pyrexia), pulse 60. Respirations 20. This was diagnosed as a crossed hemiplegia due to neoplasm in base of pons.

Post mortem. Carcinoma hilum of right lung. Secondary nodules with haemorrhages in floor of left lateral ventricle and pons.

With Signs and Symptoms of Spinal Cord Lesion.

1. Male, aged 56. Seven months ago patient caught a 'chill', since when he had had persistent cough with a small amount of sputum. For three months severe pain was present in the right side of chest with exacerbations, especially on coughing. Pain and cough were both better after resting in bed. Six weeks ago he noticed some nodules on the chest-wall, and pain along right sciatic nerve. For one month he had pain in the back and dragging of the legs (first left, then right), complete loss of use of the legs occurring after a few days. Retention of urine was also present. He lost 3½ stone in six months.

On examination. Flaccid paraplegia, with absent sensation below umbilical level. Impaired percussion note and diminished breath sounds right lower lobe, scattered rhonchi. Subcutaneous secondary nodules. Irregular pyrexia. Diagnosis:—Paraplegia. Secondary carcinoma.

Post mortem. Carcinoma hilum left lung, involving right and left bronchi. Bronchiectasis. Metastases in eighth and ninth thoracic vertebrae pressing on the cord with distinct softening of tenth thoracic segment of cord. Involvement of fifth lumbar vertebra and twelfth thoracic and first lumbar nerve roots.

2. Female, aged 53. For three months patient had pain in back, spreading round the body like a girdle at about the level of twelfth dorsal vertebra. For one month there had been gradual loss of power in both legs, and a 'sciatic' pain first in right leg, then the left. During the last two weeks retention of urine occurred.

On examination. Fundi normal. Flaccid paraplegia. Anaesthesia below D. 7 with slight band of hyperaesthesia above this level. Cerebrospinal fluid normal. Signs of cavitation in apices of both lungs.

Post mortem. Carcinoma of bronchus to right upper lobe with secondary nodules throughout lungs. Metastases in body of eighth thoracic vertebra (with considerable collapse of vertebra), in the twelfth thoracic vertebra, and in the suprarenals. Thrombosis of the iliac veins of both sides.

3. Male, aged 61. For one month patient had pain in the left shoulder. Subsequently there was pain and numbness and swelling of the feet and legs. Loss of power, first in the right leg and then in the left leg, soon followed. For fourteen days there was incontinence of urine.

On examination. Flaccid paraplegia. Abdominal reflexes present. Loss of sensation below level of groins and iliac crests. Slight crepitations at base of right lung. Temperature 98° F. Pulse 90. Respirations 20. Wassermann reaction negative.

Post mortem. Nodule of scirrhous carcinoma occupying superior mediastinum and glands above left bronchus. Haemorrhagic secondary nodule occupying first and second lumbar segments of the spinal cord with haemorrhagic softening of remainder of lumbar and upper sacral cord. White secondary nodule in the right lobule of cerebellum.

With Acute Onset.

1. Female, aged 42. Six months ago patient had an acute attack of 'influenza'. There were vague aches and pains all over the body, general malaise, headache, shivering, and vomiting. She improved after a few weeks in bed, but on getting up noticed dyspnoea on exertion, a dry cough, pain in left chest and down left arm. For one month a small lump had been noticed in the axilla.

On examination. Wasting, axillary glands, dullness and diminished breath sounds left chest. Terminal flaccid paralysis.

Post mortem. Primary carcinoma of hilum of left lung with fibrino-haemorrhagic pleurisy. Metastases in vertebral column, &c.

2. Male, aged 59. Two months ago patient had a sudden attack of shivering, cough, pain in right side, and pyrexia. The severe attack lasted ten days and was diagnosed by his doctor as pneumonia of left upper lobe. There was a history of vague occasional pains in the chest for some weeks previous to the acute onset. Patient gradually recovered from the attack, but a few weeks later noticed hoarseness, wasting, and slight jaundice.

On examination. Stony dullness and absent breath sounds over right lung. Nodular enlargement of liver. Left vocal chord paralysis.

Post mortem. Primary carcinoma of hilum of left lung. Purulent bronchopneumonia left upper lobe.

3. Male, aged 52. Nine months ago patient had acute pleurisy, from which he recovered. A few weeks later he had a slight cough, and dyspnoea. Three months ago he noticed a transient swelling of left leg, and then of right leg. For one month left arm had been swollen.

On examination. Dullness and distant tubular breathing whole of left chest. Purulent effusion aspirated. Right axillary vein thrombosed and palpable.

Post mortem. Primary carcinoma of left lung. Thickened pleura over whole of left lung, with numerous adhesions.

Oedema as a Prominent Sign.

1. Male, aged 50. The patient had a chronic cough for ten years. Four months ago he 'came over giddy', his face became swollen and the veins of the neck became very prominent. Patient thought he would choke. This condition continued and a few weeks later the left arm became swollen. Shortly after this the sputum became blood-streaked. For one month the patient had dysphagia and pain in the chest.

On examination. Swelling of the face, neck, and left arm, with prominent veins over the trunk on both arms. Swelling of both optic disks. Dullness over the right upper lobe and scattered rhonchi throughout both lungs. Irregular pyrexia.

Post mortem. Carcinoma of right bronchus invading mediastinum, pressing on and invading the superior vena cava. Thrombosis of the superior vena cava, right and left internal jugular and subclavian veins, left iliac and femoral veins. Numerous metastases.

2. Male, aged 65. The patient had winter cough for many years. Twelve months ago, when stooping, patient felt as if the blood was rushing to his head. Since that time he had to give up stooping. For nine months dyspnoea was noticed on exertion and the voice had become hoarse a few months later. Six months ago patient had a slight attack of pleurisy with blood-stained sputum for a few days. One night four months ago patient woke up with an attack of severe dyspnoea. For four months there had been swelling of the face and neck so that it was impossible to wear a collar.

On examination. Wasting. Cyanosis. Swelling of face and neck. Enlarged cervical glands. Oedema of feet. Right pleural effusion.

Post mortem. Carcinoma of bronchus to left lower lobe filling mediastinum, surrounding and compressing the branches of the arch of the aorta and the corresponding veins. Carcinomatous infiltration of cervical glands.

3. Male, aged 44. For six months patient had a cough. Six weeks ago he was found unconscious in a room full of coal gas. His face was then swollen. For four weeks patient noticed marked swelling of the left side of his face and neck. He then suffered from dyspnoea. A week later the swelling extended to the left upper limb, and ultimately to the right arm and to the chest-wall.

On examination. Cyanosis, venous congestion, and oedema of face, neck, chest-wall, and both upper limbs. Dullness over the right chest below fourth rib. Generalized bronchitis. Venesection produced marked temporary relief.

Post mortem. Carcinoma of hilum of right lung infiltrating mediastinum. Invasion with obstruction of superior vena cava. Thrombosis of both internal jugular and axillary veins. Right pleural effusion.

Pain as the Presenting Symptom.

1. Male, aged 53. Six months ago patient suffered from a sharp gripping pain across both loins. The pain persisted at all times with frequent very severe exacerbations. After a few weeks, pain extended down the front of the right thigh. Three months later pain occurred in the right chest, and at about the same time the voice became husky and the patient noticed loss of weight. There was no cough.

On examination. A wasted man, with inspiratory stridor and foetid breath. Dullness and bronchial breathing over and to right of manubrium sterni. Diminished breath sounds right lower lobe. Tender lump in epigastrium, and also over lumbar vertebrae. Blood-streaked sputum in hospital.

Post mortem. Carcinoma of right bronchus, adherent to trachea and infiltrating pericardium. Metastases in liver, femur, lumbar and sacral vertebrae, and several ribs (with spontaneous fractures).

2. Male, aged 56. For nine months the patient had suffered from pain in the right ankle and foot and along the peroneal tendons. Pain was worse at night and might radiate up to the lower abdomen. Shortly after the onset weakness was noticed in the left leg. For seven months the patient had increasing constipation with loss of weight.

On examination. No abnormal signs detected in the lungs. Distended veins present over the abdomen. Flaccid paralysis and wasting of left leg. Carcinoma of the rectum was suspected. Sigmoidoscopy showed a circular constriction 20 cm. from anus but no growth. Barium enema showed delay at splenic flexure.

Post mortem. Small scirrhous carcinoma surrounding bronchus to left lower lobe. Mass of growth in the pelvis, infiltrating the body of the left iliac bone, and body of first sacral vertebra, completely surrounding the nerves of the left side of the pelvis. Metastases in the suprarenals, liver, and abdominal glands.

3. Male, aged 35. For twelve months the patient experienced a dull pain and stiffness of lower back, which commenced about one hour after starting work, and was at first relieved by lying down. Later the pain became continuous and in hospital the patient complained of excruciating exacerbations of pain which prevented the slightest movement. The pain occasionally radiated down both thighs. During the last few months the voice had become husky and there was some wasting.

On examination. Sonorous rhonchi scattered throughout both lungs. Afebrile. Tenderness over the lumbar spine.

Post mortem. Mass of growth occupying the hilum of left lower lobe. Metastases in the lumbar vertebrae pressing on the cord, and involving nerve roots and psoas muscles on both sides.

With Early Superficial Metastases.

Female, aged 54. Five years ago patient had a severe blow on the skull. Four years ago she noticed a small lump on the head about the size of a pea. This kept the same size for six months and then began to grow larger. During the last six months she had cough, wasting, night sweats, and a little sputum. Six weeks ago the lump was incised, but only a little blood was obtained and the wound healed rapidly.

On examination. Dullness and absent breath sounds left lower lobe. Glands of neck. Lump in skull fixed to bone and skin. Removal of lump in skull and glands in neck. Microscopic sections showed tubular secondary carcinoma with a bronchus as probable primary site. After operation patient had haemoptysis. Paracentesis thoracicis revealed clear pleural effusion. Temperature 98–100° F. Pulse 120. Respirations 30.

Post mortem. Carcinoma left bronchus. Secondaries in skull, liver, suprarenals, vertebrae. Before autopsy the diagnosis was sarcoma of skull. The superficial secondary deposit was apparently present for 3½ years before the lung symptoms developed.

Male, aged 13. For eighteen months patient had wasted. Fourteen months ago he noticed superficial lumps in the chest-wall. There was no pain, no cough, no dyspnoea. Examination of the chest at that time showed dullness and diminished breath sounds over right lung. Radiography indicated neoplasm. X-ray treatment caused great improvement; disappearance of the subcutaneous secondaries and of dilated veins of chest-wall. Six months ago subcutaneous metastases reappeared in the same place. From that time patient complained of pain in chest, cough, and dyspnoea.

Post mortem. Carcinoma right lung. Numerous metastases.

Onset with Haemoptyses.

Male, aged 43. Nine months ago patient had several small haemoptyses, followed by blood-streaked sputum for a few days. Two months later he caught a cold and was troubled by a hacking cough and substernal pain. Wasting was also noticed.

On examination. Engorged veins, neck, arms, and abdomen. Dullness and absent breath sounds right lower lobe. Tumour left axilla.

Post mortem. Carcinoma right lower lobe with secondary mass in left axilla.

Onset with Aphonia.

Male, aged 60. Five months ago patient caught a cold and lost his voice. Ever since has had dyspnoea on exertion, hacking cough, and occasional sternal pain.

On examination. Moist sounds throughout lungs. Some dullness to left of sternum. Paralysis left vocal cord.

Post mortem. Carcinoma of hilum of left lung replacing bronchial glands and involving oesophagus, trachea, and descending arch of aorta. Purulent bronchitis both lungs.

Dysphagia as an Early Symptom.

Female, aged 50. Five weeks ago patient found herself unable to drink anything, and choked in attempting to do so. At that time also had pains all round the chest and neck, some dyspnoea, and a severe dry cough. Patient felt as if she were going to faint when lying down—had to sit up. Recently nausea and anorexia were experienced.

On examination. Wasted. Orthopnoea. Right and left supraclavicular glands enlarged. Bronchial breathing over right lung with dullness at base. Scattered rhonchi throughout lungs. Temperature 98–100° F. Pulse 110–20. Respirations 30. X-ray showed oesophageal obstruction at about the level of D 4. Pleural effusion right.

Post mortem. Carcinoma of right lung surrounding bronchus to right lower lobe. Great kinking of oesophagus by growth without invasion of its muscularis. Bronchitis and bronchiectasis. Pleural effusion right.

Simulating Simple Empyema.

Male, aged 30. Two months ago there was a sudden onset of pain in the right hypochrondrium associated with shivering and vomiting. Three days later cough and expectoration and dyspnoea commenced. The shivering attacks continued.

On examination. Wasted. Dilated abdominal veins. Bronchial breathing and increased vocal resonance over right apex posteriorly. Below this dullness and diminished breath sounds. Temperature 99–100° F. Pulse 120. Respirations 28. Blood count: Leucocytes 27, 840; 92 per cent. polymorphs. On needling the chest, pus was found and a rib subsequently resected.

Post mortem. Carcinoma lower lobe right lung. Solid oedema and gangrene right upper lobe. Metastases in 12th thoracic vertebra and 8th and 9th right ribs. Right-sided empyema.

Simulating Simple Pleural Effusion.

Male, aged 38. Sixteen months ago cough and dyspnoea commenced. Twelve months ago patient entered a chest hospital, with signs of pleural effusion. After six weeks in bed, 40 oz. clear amber fluid were withdrawn and 200 c.c. oxygen inserted. The patient improved and was up for two months, after which he again took to bed. Then he had severe pain in the right side. Fluid again withdrawn from chest.

On examination. Stony dullness and absent breath sounds over right chest. Two subcutaneous nodules to right of sternum. Radiography showed neoplasm and fluid. Temperature 98–99° F. Pulse 100. Respirations 26.

Post mortem. Carcinoma of right bronchus. Pleural effusion.

Simulating Primary Bronchiectasis.

Male, aged 42. Two years ago the patient had pleurisy. Ever since he had a bad cough on and off with moderate amount of sputum. Six months ago had a cold, and was in bed four days with cough, slight haemoptysis, and dyspnoea. The cough persisted, was severe and often brought on vomiting. Wasting and night sweats were noticed. For one month large quantities of offensive sputum were expectorated, especially in the morning. Pain was felt on left side and across the chest.

On examination. Clubbing of fingers. Tubular breathing left upper lobe. Remainder of left lung dull with absent breath sounds. Hyperaesthesia base of left lung. On needling, pus was found. Resection of rib was performed and

a large bronchiectatic cavity drained. Radiography showed consolidation with abscess formation. Temperature 98–101° F. Pulse 80–110. Respirations 24–30.

Post mortem. Carcinoma of left bronchus with extensive bronchiectasis.

Simulating Aneurysm.

Male, aged 35. Ten months ago patient had sudden onset of pain over the heart and over the bases of both lungs. He gradually became worse. For eight months he had cough and expectoration, the latter was blood-stained on five or six occasions. Five months ago the speech became husky. For four months the pain had been almost continuous, but worse on exertion and at night, but relieved by sitting up in comfortable chair. The patient had lost 10 lb. in weight since the onset of illness. Eight years ago he had a laparotomy performed for ascites, and cirrhosis of the liver was found.

On examination. Wasted. Husky voice. ?Tracheal tug. Pulses equal. Dullness in first and second left spaces anteriorly. Dullness and diminished breath sounds left base. Spleen just palpable. Blood-pressure, right 125, left 115 mm. of mercury. Abductor paralysis left vocal cord. Wassermann reaction negative, even after provocative N.A.B. X-ray examination suggested aneurysm. Temperature 98–99° F. Pulse 80. Respirations 24.

Post mortem. Carcinoma of hilum of left lung, obliterating left bronchus and invading the mediastinum. Blood-stained pleural effusion left. Constriction of arch of aorta by adherent growth. Fibrosis of liver and spleen with perisplenitis. No aneurysm.

Male, aged 52. For two months patient had dyspnoea, cough, and slight occasional expectoration. Pain was felt in left lower chest and deep to sternum. For one month he was unable to sleep lying down. Patient had lost weight.

On examination. Apex beat was in 6th space, internal mid-clavicular line. The second aortic sound was sharp and metallic. Harsh systolic murmur at base of heart. Left chest hardly moves—dull and absent breath sounds. Dilated veins over abdomen. Left chest needled—nil found. Tracheal tug. Wassermann reaction negative twice. Temperature 98° F. Pulse 90. Respirations 24. X-ray showed aneurysm of aorta—pulsation definitely seen. Largely on the radiographic evidence a diagnosis of thoracic aneurysm was made.

Post mortem. Carcinoma left lung, also occupying posterior mediastinum. Adhesions of growth to posterior wall of aorta. No aneurysm.

Remissions and Delayed Diagnosis.

Male, aged 49. Twenty-two months ago patient had influenza and bronchitis and was away from work for one month. A dry cough persisted and was worse at night. For eighteen months he had had weakness, anaemia, and a dull ache at the bottom of the back. His condition was diagnosed as phthisis and he was treated at a sanatorium for three months, where he improved considerably. He then returned to work, but still felt unwell. Nine months ago he saw a specialist, who diagnosed influenzal catarrh and gave a course of vaccines. Seven months ago patient had a severe cold which persisted. Has lost two stone in weight.

On examination. Dilated veins over chest and abdomen. Slight clubbing of fingers. Relative dullness and bronchial breathing right upper lobe. Diminished breath sounds right lower lobe. Sputum negative for tubercle bacilli. X-ray shows neoplasm of superior mediastinum. Temperature 98° F. Pulse 90. Respirations 24.

Post mortem. Carcinoma of hilum of right lung. Bronchiectasis.

Tuberculosis and Carcinoma of Lung.

Male, aged 40. The patient was brought in stuporous with a history of one month's headache and malodorous breath. He died in a few hours.

Post mortem. Carcinoma of hilum of right lung invading the main bronchus and spreading into right upper lobe. Fibrosis of right upper lobe with tubercular pneumonia and calcareous nodules in apex. A section from the hilar region of the lung showed one half to consist of growth and the other half to consist of tubercular lung. Section through right upper lobe showed fibrocaseous tubercular bronchitis and peri-bronchial pneumonia.

Syphilis and Carcinoma of the Lung.

Male, aged 37. Three and a half years ago patient was operated on for gall-stones, but multiple gummata of liver found. Wassermann reaction was positive. For three months he had a cough, sputum, haemoptysis, pain right chest, loss of weight.

On examination. Dilated veins over chest. Dullness and diminished breath sounds right lung, with scattered rhonchi throughout left lung. Oedema left arm, and palpable thrombosed left internal jugular vein.

Post mortem. Carcinoma of hilum of right lung extending to anterior half of right upper lobe. Syphilitic and interstitial pneumonia of remainder of upper lobe of right lung. Collapse of right lower and middle lobes. Focal syphilitic fibrosis of liver and left kidney.

Summary.

This study comprises a clinical and pathological investigation of 139 cases of primary carcinoma of the lung.

1. The pathology of carcinoma of the lung is briefly described and the most important pathological complications, including metastases, are considered.

2. The symptomatology of carcinoma of the lung is described in detail, and an attempt is made to correlate symptoms with their pathological basis.

3. The diagnosis and differential diagnosis of carcinoma of the lung is considered in detail. The different types of errors revealed by autopsy examinations are classified, and indications for their avoidance are deduced from a retrospective study of the clinical aspects.

4. Prognosis and treatment are briefly considered.

5. Statistical evidence of the increased incidence of primary carcinoma of the lung is put forward.

6. Evidence is advanced in favour of this being a real increase independent of improvements in pathological or clinical diagnosis.

7. Statistics are given to show that the increase is unaccompanied by any corresponding increase in the total carcinomata admitted to the London Hospital.

8. The aetiology of primary carcinoma of the lung is considered, and it is concluded that irritation in one form or another is probably an important factor.

9. Several characteristic cases are described to illustrate some of the main points of the paper.

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THE TREATMENT OF EXPERIMENTAL TUBERCULOSIS BY CALCIUM ADMINISTRATION[1]

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THE treatment of tuberculosis by the administration of calcium has been extensively adopted in recent times with results that are not in harmony. Fourcroy, as early as 1783, recommended calcium chloride in the treatment of scrofula, and from that time onwards a continuous stream of clinical observations has appeared. Kahn (1), in 1914, after reviewing the literature, came to no definite conclusions as to the value of such treatment. A few writers have stated that they have found no benefit (2, 3, 4), but most of the clinical reports have been exceedingly optimistic (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and others). In none of these papers have the opinions been supported by control observations on cases of similar type and severity under identical general treatment; and until such criteria are adopted for assessing the value of calcium treatment, evidence of this character has no precise value. Recent papers by Hartwich-Borrmann (19) and Pinkhof (20) on the treatment of sanatorium patients by oral and intravenous calcium administration serve to emphasize this difficulty, although both agree that such treatment has a sphere of usefulness in cases of the exudative type.

The early work was entirely experimental and speculative, but more recently the use of calcium is supposed to have been placed on a sounder basis by certain new observations. It is known that when a tuberculous lesion becomes arrested calcification always occurs, and it has been held that calcium administration should therefore favour arrest of the disease. Maver and Wells (21), however, have rightly insisted that there is no evidence to show 'that calcification favours rather than follows healing', though they agree that a tuberculous focus when calcified is less likely to break down and liberate living tubercle bacilli. Certain statistical evidence purports to show that the mortality from pulmonary tuberculosis is lower in districts where the soil is rich in calcium salts (22, 23) than in others, and that it is low among workers engaged in trades where dust containing much calcium is inhaled (24, 25, 26, 27, 28, 29, 30, 31, 32, 33). Many of the districts with soils rich in calcium, however, have climates favourable to the patient; further, it has not been clearly shown how far general hygienic and economic factors, particularly density of population, confuse the issue, and therefore this evidence has little value.

[1] Received November 20, 1928.

It has been claimed repeatedly that workers in lime are relatively immune to tuberculosis, though exact data are scanty. Recent statistics for England and Wales, published in the Registrar General's Decennial Supplement for 1921 (34), do not support this claim. The occupational group comprising lime-burners and foremen and other skilled or unskilled workers employed in making lime, whiting, cement, plaster, artificial stone, and concrete is exceedingly healthy; the ratio of the comparative mortality figure (C.M.F.) from all causes to that of all occupied and retired males between the ages of 20 and 65 years is 0·717. Only 13 out of 164 occupational classes show a lower ratio than this. The C.M.F. ratio for all forms of tuberculosis for this class is 0·651, and for respiratory tuberculosis 0·706. Moreover, the ratio for phthisis is less in 28 out of the 164 classified occupations. In the group comprising limestone miners and quarriers the C.M.F. ratio for all causes is 0·918, for all forms of tuberculosis 0·971, and for respiratory tuberculosis 1·001; and it should be emphasized that the ratios for phthisis and all forms of tuberculosis are greater than those for any other causes of death, except influenza and accident. The ratio for phthisis is about halved for workers in igneous rock, and about doubled for sandstone workers. The special risk from uncombined silica associated with the latter occupation is, of course, responsible for the greater mortality. In the group comprising limestone masons, cutters, and dressers, the C.M.F. ratio for all causes is 1·197, for all forms of tuberculosis 1·769, and for respiratory tuberculosis 1·735; and here the tuberculosis ratios are greater than those for any other causes of death except peptic ulcer. Among plasterers the C.M.F. ratio for all causes is 1·011, for all forms of tuberculosis 0·861, and for respiratory tuberculosis 0·882.

These figures, for the four occupational groups most exposed to lime dust, show that the proportion of the total mortality which is due to respiratory tuberculosis among such workers is similar to or greater than that among the population in general. The ratios for respiratory tuberculosis and those for all forms of the disease are similar, but no definite conclusions are warranted, as the latter are based on a few deaths only, and the probable error is therefore great. It might be anticipated, however, in a larger series of statistics, that the ratios for respiratory tuberculosis would be considerably less than those for all forms of the disease if calcium inhalation has any prophylactic value.

Lime-workers inhale considerable amounts of dust rich in calcium, and it is known that animals under similar conditions absorb this calcium so that an excess is found in their lung-tissue with its lymphatic connexions, and also in the blood (35). Before any sound basis for the curative treatment of tuberculosis by calcium salts can be maintained it must be shown that such conditions facilitate the healing of tuberculous lesions, or alternatively that they prevent the implantation and growth of tubercle bacilli in the tissues. Many attempts have been made to determine in experimental animals whether a persistent increase in the amount of calcium in the body fluids and tissues is beneficial in tuberculous infections. Experiments have been made on guinea-

pigs and rabbits by administration of calcium either as an inhalation of dust (32, 35, 36, 37, 38, 39,) or by oral, subcutaneous, or intravenous methods (2, 21, 40, 41, 42, 43, 44, 45, 46, 47). The literature shows that completely negative results have been found, except with treatment by inhalation. A few authors have claimed some benefit from oral or intravenous treatment of guinea-pigs and rabbits (40, 41, 43, 45, 47) but in every case the experiments were unsatisfactory; either the treated animals were too few and the controls inadequate, or a bacillary culture of very low virulence was inoculated. In Pelouze and Rosenberger's work (45) the strain of organism was of such low virulence that experimental lesions produced by inhalation inoculation commonly healed; further, these investigators do not state the exact dose of organisms administered and give no figures of the relative lengths of life of either control or experimental guinea-pigs.

Experimental work gives no support to the view that oral administration of calcium has beneficial effects in tuberculosis. Nevertheless, we know that calcium administered orally to rabbits is absorbed in sufficient quantity and at a sufficiently rapid speed to produce a considerable rise in the blood calcium, provided that large doses are given (48). The doses used by investigators in the treatment of experimental tuberculosis have not been sufficient to produce this effect. It is not unlikely that large amounts might yield results more comparable with those that are claimed for inhalation treatment with calcium hydroxide and carbonate.

The difference in the results obtained by inhalation and oral administration appears to be due to the difference in the rate of absorption from the gut and from the lung capillaries. As the lungs are almost always heavily diseased in animals with experimental tuberculosis, inhalation has the added advantage of being a local therapy. All workers who have studied the effect of calcium dust inhalations, except Nagai (37), are agreed that in general the lesions calcify more readily and the animals live rather longer than controls. In every case, however, the beneficial effects are slight, and in none has arrest been found. It is obvious, though, that calcium inhalation in experiments extending over a few months is not comparable to the dust which lime-workers inhale over a period of years. Moreover, lime-workers are certainly not infected with tuberculosis in one massive dose, as in the case of experimental animals. I think that these slight beneficial effects deserve some recognition when the differences in the conditions of experimental and natural infection and in the relative periods and intensities of calcium inhalation are taken into consideration. Clinically, treatment by inhalation is disappointing. In phthisis no striking results have been obtained (10, 30, 49, 50, and 51), though, as with almost any other treatment, temporary benefit usually occurs.

Recent investigations have thrown considerable light on the changes in calcium metabolism occurring during the disease. Earlier observers, led by the French school, held that in phthisis there was a progressive demineralization due to increased excretion (13, 15, 52, 53, 54, 55); this has been proved incorrect

(56, 57, 58, 59, 60, 61), except possibly for those advanced cases in which intestinal ulceration is present. It has been shown, on the other hand, that caseous tuberculous tissues contain many times the normal amount of calcium, even when there is no gross calcification (21, 62, 63, 64). This deposit of calcium in the lesions implies demineralization elsewhere, unless the amount absorbed and retained by the organism is increased, and for this there is no evidence. The calcium must be withdrawn from the tissue fluid and ultimately the blood and other tissues; it is deposited in the caseous foci in the form of insoluble phosphate, carbonate, and fatty acid soaps. Matz (65), Teplitz (66), Schoenheit (67), Greisheimer and Van Winkle (68), and Brockbank (69) have shown in phthisical patients with active extending disease that the serum calcium falls. It is difficult to assess precisely the value of their evidence, because secondary infection was not excluded, and it is known that this in itself can produce a fall in serum calcium. But recently it has been shown (70) in experimental tuberculosis in rabbits, conducted under conditions in which secondary infection could be excluded, that a similar fall in blood calcium occurs; this decrease in serum calcium was related to the degree and extent of caseation, and so presumably to the calcium content of the lesions. It is evident, therefore, that the rate at which caseation progresses is a deciding factor in determining whether a fall in serum calcium occurs. If caseation is rapid, then the withdrawal of calcium from the blood is also rapid; if caseation is slow, the drain is more gradual and no fall may be found. The latter might well account for certain of the results obtained by investigators who have claimed that no fall occurs in the serum calcium in phthisis (71, 72, 73, 74, 75, 76) and would account for the steady serum calcium found by Brockbank (69) in incipient, abortive, and fibroid cases. Recently I have shown (77) that a purely local caseating focus in experimental animals is invariably accompanied by a slight rise in serum calcium, and this suggests that in these cases a compensatory mechanism is at work to facilitate the supply of calcium for the limited lesion. In other words, the level of the serum calcium is an index of the ability of the organism to maintain the supply of calcium required by the diseased tissues. It has not been determined whether this conception holds good in clinical surgical tuberculosis when the lesion is limited and not infected by secondary organisms.

Such considerations, based upon experimental work, afford a clearer insight into the significance of serum calcium estimations in tuberculosis and of calcium administration in clinical practice. Since all forms of tuberculosis are accompanied by caseation, it is obvious that if the disease progresses sufficiently rapidly the serum calcium will be lowered, and a relative calcium deficiency obtain. Under such conditions it is rational to supply an excess of the element to the patient, and so attempt to prevent the continuous drain on the tissues. This treatment merely compensates for a pathological demand, and no clear evidence exists to show that the calcium exerts any direct action on the course of the disease.

Experimental.

The present paper deals with the results obtained in experimental tuberculosis in the rabbit by intravenous treatment with calcium chloride. 0·001 mg. of a fourteen days old serum culture of a virulent bovine strain was inoculated into the peritoneal cavity of each of fourteen animals. Eight were kept as controls. The remaining six were given intravenous injections of a calcium chloride solution daily. The dose during the first week was 5 mg. of Ca. per kilo bodyweight and afterwards twice this dose. Forty-eight injections were given in those animals which survived the longest. The solution used contained 3·5 mg. Ca. per c.c. and was prepared from arsenic-free Ca. $(OH)_2$ and HCl in the requisite proportions; this was diluted with sterile distilled water to the required bulk and the solution tested for neutrality and stored in paraffin-sealed bottles.

The initial weights, the lengths of survival after inoculation, and post-mortem findings for the control animals are shown in Table I; and for the treated animals, together with the total number of injections, in Table II. The average length of survival after inoculation in the control rabbits was fifty days, and in the treated forty-six days. No differences were found in either the extent or character of the disease in the two groups at post-mortem examination, except that in Rabbit 67 there was considerably less disease in the lungs than usual. In this animal the peritoneal involvement, however, was very severe, and death occurred in less than the average time after inoculation.

In every case treatment was pushed to the limit of safety, and the animals were receiving approximately seven times more Ca. per kilo than in experiments recorded by Massini (47) and about twenty times more per kilo than in the clinical cases described by Brockbank (69).

These results show that treatment by intravenous administration of calcium has no effect in prolonging the course of the disease in a moderately rapid experimental infection; and it is evident that experimental evidence is lacking to suggest that calcium exerts a direct therapeutic action on the course of the disease.

The work on which this paper is based has been concluded during the tenure of the Ernest Hart Memorial Scholarship of the British Medical Association.

TABLE I.

Rabbit No. and Sex.	Initial weight in kilos.	Length of survival after inoculation in days.	Post-mortem appearances.
62 ♂	2·58	45	Small lesion in the abdominal wall in the track of the inoculating needle. Peritoneum extensively involved with opaque discrete tubercles, and one larger caseous area in the mesentery. A few cysticerci in the omentum and liver. Lungs show many caseous foci. Bronchial glands and retrosternal glands enlarged.
64 ♀	2·26	82	Diaphragmatic peritoneum shows several caseous nodules up to $\frac{1}{2}''$ in diameter. Visceral peritoneum less affected than usual, but shows scattered caseous tubercles up to $\frac{1}{8}''$ in diameter, in the mesentery particularly. Numerous caseous areas in both kidneys (T. Bac. +) and epididymes. Lungs show widely confluent caseous disease (T. Bac. +).
66 ♀	1·95	74	Small local lesion in the abdominal wall. Several caseous tubercles $\frac{1}{2}''$ in diameter on the under surface of the diaphragm, and many smaller ones over the visceral peritoneum. Few small caseous foci in the renal cortices. Lungs show very extensive confluent caseous disease (T. Bac. +).
68 ♂	2·52	48	Generalized miliary disease in the peritoneum. Both renal cortices show a few small isolated opaque tubercles, and the lungs fairly extensive caseous areas.
72 ♂	1·96	44	Diffuse miliary disease throughout the peritoneum, not, however, of extreme numerical severity. Omentum reddened, enlarged, and adherent to the intestines. Both kidneys show one or two small opaque tubercles. Lungs (weight = 75 grm.) extensively affected with confluent caseous foci.
74 ♂	1·92	54	Miliary disease throughout the peritoneum. Omentum caseous. Lungs (T. Bac. +) widely involved with confluent caseous foci.
76 ♀	1·40	33	Small caseous lesion in the abdominal wall. Generalized miliary disease in the peritoneum and lungs.
78 ♂	1·61	25	Very extensive miliary disease, confluent in places, throughout the peritoneum. Omentum caseous. A few minute tubercles in both renal cortices. Both lungs packed with caseating miliary tubercles.

TABLE II.

Rabbit No. and Sex.	Initial weight in kilos.	Total number of injections.	Length of survival after inoculation in days.	Post-mortem appearances.
61 ♀	2·18	48	71	Small deep-seated local lesion in abdominal wall. Extensive peritoneal disease, with caseous lesions up to ½″ in diameter. Omentum caseous. Several caseous foci in both kidneys. Lungs widely diseased with coalescing caseous lesions.
63 ♀	1·85	35	36	Generalized tuberculosis. Submiliary disease throughout the peritoneum. Omentum caseous and adherent to intestines. Nil in the kidneys, naked eye. Both lungs extensively diseased with conglomerate and isolated caseous foci.
65 ♀	2·61	48	77	½″ circular ulcer in the anterior abdominal wall, and a deep-seated caseous lesion in the track of the inoculation puncture. Generalized tuberculosis, with very extensive caseation, in the peritoneum and lungs (T. Bac. +). Bronchial glands enlarged.
67 ♀	1·85	36	37	Small lesion in the abdominal wall. Very extensive submiliary disease throughout the peritoneum. Considerably less disease than usual in the lungs (T. Bac. +); tubercles few, isolated, caseous, and about 2 mm. in diameter.
69 ♀	1·70	32	33	Generalized miliary disease throughout the peritoneum. Omentum enlarged and caseous (T. Bac. +). Many semi-translucent miliary tubercles in the lungs (T. Bac. +). Retrosternal glands enlarged and caseous.
71 ♂	1·16	20	21	Very extensive miliary disease in the peritoneum and lungs. Omentum enlarged and acutely inflamed. No naked eye changes in the kidneys.

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SOME CLINICAL ASPECTS OF MUSCULAR EXERCISE[1]

By FRANK W. LAW

With Plate 17

Muscular exercise, considered from a medical aspect, falls naturally into the two main divisions first defined by Plato—active and passive; the former involving the exercise of will power in its achievement, the latter being independent of will power and consisting merely in the involuntary exercise of the body musculature by such means as massage or machines. Active exercise may take one of two forms: exercise of effort, consisting of a short period of intense exertion such as the lifting of a heavy weight, and exercise of endurance, when the exertion, though perhaps strenuous, is prolonged over a considerable period, and involves a far greater output of mental energy, and a response by the various systems of the body as a whole, for its achievement. The last form of exercise will be dealt with here, and one particular branch of athletics, namely, rowing—perhaps the most strenuous and exacting branch—used in illustration.

The Assessment of Physical Fitness.

The routine at present adopted for the examination of prospective and actual members of the Cambridge University Crew is as follows: A careful history of the athlete is first taken which includes a record of previous illnesses and of any familial or hereditary disease. This is, as might be expected, usually irrelevant or negative; since a man definitely unsound would not have proceeded far enough along the athletic road to have reached the stage which necessitates the examination in question. The weight, height, and stem-length are measured, and the resting pulse-rate and blood-pressure recorded. The apex beat, area of cardiac dullness, and character of heart sounds are noted, and the condition of the lungs is examined by inspection of the chest, percussion, and auscultation. The circumference of the chest is measured and the vital capacity estimated by means of a spirometer.

Two short tests are then applied: the dumb-bell test, which consists in causing the subject to do hard dumb-bell exercise for about 1 minute, when the effect upon the pulse-rate is noted, including the time occupied by its return to normal or below; and the '40 mm. Hg. U-tube test'. The latter is one in use at the present time in the examination of candidates for the Royal Air Force, and

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consists in counting the pulse-rate in 5-second periods while the subject is maintaining a column of mercury which he has blown up to a height of 40 mm.

As regards conclusions from these tests. In the first case the pulse-rate of a healthy fit man should return to normal in less than two minutes. If such be the case it is usually found that it continues to fall to a level below the resting level for a short time, rising then to the resting level in the course of a further minute or so. The extent of the rise is also of importance, for although no definite figures may be considered as 'normal', the rise should not be more than one of 20 to 30 beats per minute. The test is a valuable one, and is, for instance, an excellent measure of the extent of recovery from a passing indisposition such as a mild attack of influenza, which so frequently occurs during the course of training for an athletic contest. In one case, which occurred during training for the University Boat Race, the subject who was previously within normal bounds in his response to the test was found to show, a few days after an attack of influenza, a rise in pulse-rate of between 30 and 40 per minute, and a period of over 3 minutes before returning to his normal rate.

In the U-tube test the healthy subject should hold the column up for at least 50 seconds, less than 40 being considered unsatisfactory. The pulse-rate should either remain unaffected or rise from, say, 72 to 96. A large increase, up to the neighbourhood of 140, indicates abdominal venous pooling and is unsatisfactory; whereas marked physical inefficiency is indicated by a pulse-rate which rises to a high level very rapidly—that is, in the second or third 5-second period—and then falls to normal or below normal. The result of the test is recorded as follows: Time during which the column is maintained; number of beats per 5-seconds, resting, in sitting position; number of beats in each subsequent 5-second period; thus, 50 seconds 6/6, 6, 7, 7, 7, 9, 8, 8, 8, 8.

It is of value to record the pulse-rate and blood-pressure in testing athletic condition, noting the rise and fall of blood-pressure, and the increase in the pulse-rate, on assuming the erect from the supine posture. It is reasonable to assume that the effect on the blood-pressure, varying from +10 to −10, affects the pulse-rate, on the assumption that the heart comes to the rescue of a falling pressure by beating faster. Loss of tone in the heart and vessel walls would thus result in a falling blood-pressure, or a rising pulse-rate, or both, and only by taking both into consideration may the extent of this loss of tone be estimated. McKenzie (1) states that a difference of more than 20 beats in the lying and standing postures would, under ordinary conditions, indicate staleness, and also, presumably, unfitness.

In the Air Force examination, stress is laid upon the difference between the systolic and diastolic blood-pressure figures. While a pulse-pressure of 50 mm. is not regarded as serious *per se*, one of that figure when combined with a diastolic pressure below 70 is considered unsatisfactory when a high level of physical fitness is being aimed at.

In addition to these clinical tests, the general subjective effects of hard physical exertion upon the subject clinically fit are, of course, of great im-

portance, and an account of these effects after a bout of exercise is always taken during the course of training.

Figures and further data, of interest in connexion with the subject-matter of this section, are given in those on the After-effects of Exercise, and in the individual case-history.

Certain Phenomena Associated with Training and Exercise.

There are two processes at work in training. One is the simple development of the body musculature to perform tasks which in the ordinary way would be outside its usual powers; this is, however, not the whole of training, since a man may develop, say, his biceps muscles by dumb-bell exercises which do not, *per se*, lead to a state of general fitness of the whole body. The other is the development, in the direction of range and delicacy, of the general and mutual adjustments of the circulatory and respiratory systems to such an extent that the oxygen supply is assured and sufficient, however excessive the exercise be to which the body musculature is subjected. This is a very different and a far more important matter than the first; for sheer mass of muscle, however powerful in standing up to a strain to which it is momentarily put, is of no use for excessive or prolonged exertion unless an adequate supply of fresh oxygenated blood is assured, and it is the latter question which is the important side of all training.

The trained man then possesses, apart from mere strength, just this delicacy of adjustment which distinguishes him from the untrained. When indulging in prolonged exercise, his respiratory distress is less than that of the unfit man; his respirations are slower, his pulse-rate is slower, and his temperature does not rise so high; sweating is more delayed and less profuse; fatigue occurs later and is resisted better; the physically reassuring phenomenon of second wind happens earlier and is far less marked; and in the final tremendous effort which may be the deciding factor in achieving success (if the exercise take the form of an athletic contest) when the control of the higher centres is waning, his muscles continue to act economically and correctly in their movements towards the accurate performance of which, all the training has been directed—in other words, he 'keeps his form' to the last. Again, the effect upon him of the exercise, when this is completed, is far less than upon the untrained man, and the return to a normal condition is far more rapid and complete. The trained man is assured of regaining normal conditions however strenuous the exercise may have been, whereas the same amount of exercise may have done permanent and irreparable damage to one who indulged in it in an unfit condition. Such, in short, are the effects and advantages of judicious and complete training.

Training has an effect upon the basal metabolic rate. Benedict and Smith (2) showed that the figure was slightly lowered as a result of a course of training in the proportion of 26·0 in the untrained man to 24·4 in the trained. It would seem that the adjustments effected as a result of training cause a more efficient and economical working of the whole human machine to become possible, the

heart and lungs developing just as do the skeletal muscles. Again, just as the heart is the fundamental factor in rendering muscular exercise possible, so it is the organ which must respond to training to make excessive indulgence in exercise possible. It is strange that the idea should be prevalent that the large size of the athlete's heart is abnormal and is representative of damage to that organ; from what has been said it will be clear that the muscle performing the function of pumping blood is as capable of development in training as is one performing that of, say, flexion of a limb. Bainbridge (3), in writing on the subject, insists that the notion that a heart enlarged in the way described is abnormal is entirely erroneous. The argument usually advanced to confute the general idea outlined above, is that in the healthy man the heart is never enlarged as a result of exercise, but figures which at once disprove the correctness of this statement will be brought forward in a later section.

The influence of emotional stress upon the capability of excessive work is of interest. It is an undeniable fact that considerably more muscular effort can be made when this factor is at work; the excited shouts of spectators may, and often do, urge an athlete on to efforts which 'in cold blood' would be outside his powers, and men have been known to perform prodigious feats in the way of high jumping or lifting heavy weights when under the influence of strong emotional stress. The mechanism by which such a phenomenon occurs is not settled. Cannon (4), in his researches into the subject, attributes the fact to the discharge of adrenalin into the blood-stream. Kellaway (5), working on the same question, proved that a discharge of adrenalin can take place. There is no proof, however, that sufficient is discharged to account for the considerable effect upon the muscular capabilities which undoubtedly does occur—indeed, Gasser and Meek (6) hold that their experiments prove that excessive exercise was not accompanied by an increased output of adrenalin. The source of this extra energy developed under the influence of emotion must, therefore, remain hidden.

Another interesting phenomenon occurring during exercise is that known as second wind. Its mode and time of onset vary widely in different individuals, and do not depend upon the state of training, yet its invariable occurrence is well known to all—the look of distress disappears from the athlete's face, the respirations and pulse-rate fall, and the muscular movements become economical and easy—in a word, the whole organism 'settles down' to the work in hand and the athlete 'gets into his stride'.

There have been many explanations of this phenomenon brought forward by different writers. Perhaps the most feasible is that of Pembrey and Cooke (7), who, while admitting that pulmonary ventilation, circulation, and body temperature are all involved, attribute the phenomenon finally to a fall in the hydrogen-ion concentration of the blood. This may be due to one or more of three causes: (1) Lessened production of lactic acid and carbon dioxide in the active muscles. (2) More rapid removal of these acids from the blood. (3) More rapid oxidation of lactic acid.

Support is lent to the first of these three possibilities by the fact that, after exercise has been in progress for a short time, unnecessary movements are eliminated and others are co-ordinated better, so that acid production is less and the hydrogen-ion concentration falls. The second theory is feasible, and the process conceivably occurs, but there is little clear evidence in support of it. As to the third, may it not be that the circulatory and respiratory response and adjustment to the suddenly changed conditions need time to occur, and in the interim the oxygen supply is deficient, and lags behind the demand? It would seem that a fall in hydrogen-ion concentration is a likely explanation of the occurrence of the phenomenon of second wind, due itself to an adjustment of the circulatory and respiratory systems; support is lent to the view by the fact that second wind occurs in a far less marked fashion, and earlier in time, in a trained man than in an untrained man.

Fatigue is a phenomenon occurring after or during indulgence in strenuous exercise, alike in the trained and the untrained man. It is divisible into two kinds—general and local. The former almost certainly has its main seat in the central nervous system, and is the type met with more amongst such people as industrial workers, rather than amongst athletes. The latter is the kind with which one is here concerned. Its onset is marked by a look of distress on the athlete's face, the occurrence of increased respirations and pulse-rate, a lack of co-ordination and delicacy in the muscular movements, and a general lessening of the enjoyment previously found in the execution of the exercise; and the explanation of it is not complete. It may be due to an exhaustion of the store of energy supplied to the muscles, or to the clogging of the muscles with their own metabolic products due to a failure of continued response by the circulatory and respiratory systems. Joteyko (8) in 1904 put forward a theory that fatigue was due to the repeated receipt of impulses by sensory structures such as the muscle spindles, thus introducing a nervous element into the explanation of local fatigue. Frumerie (9) in 1903 attributed it to the repeated mechanical stimulation of joints and tendons. Up to the present, no explanation is adequate in itself; it is even possible that fatigue of the organism may originate in, and be due to, primary fatigue of the heart itself, though this would seem more readily to account for the lassitude experienced on the day after exercise rather than for the fatigue occurring actually during the exercise. A co-relation between general and local fatigue may, however, be founded on the idea that muscular metabolic products in the circulating blood cause fatigue of the central nervous system.

The Body-weight in Training.

An investigation into the body-weight during training brings to light one or two interesting facts. The body-weight of the members of the Cambridge University Crew of 1922, of which the writer had an opportunity of keeping daily record, will be referred to in particular.

It is correct to say that amongst healthy individuals undergoing a strenuous

and intensive course of training, the body-weight will reveal any ill effects this training may be having upon them, or any unfitness or 'staleness' which may occur. The problem of staleness is a most interesting one, and is not completely understood as regards causation and physiological effect, though its connexion

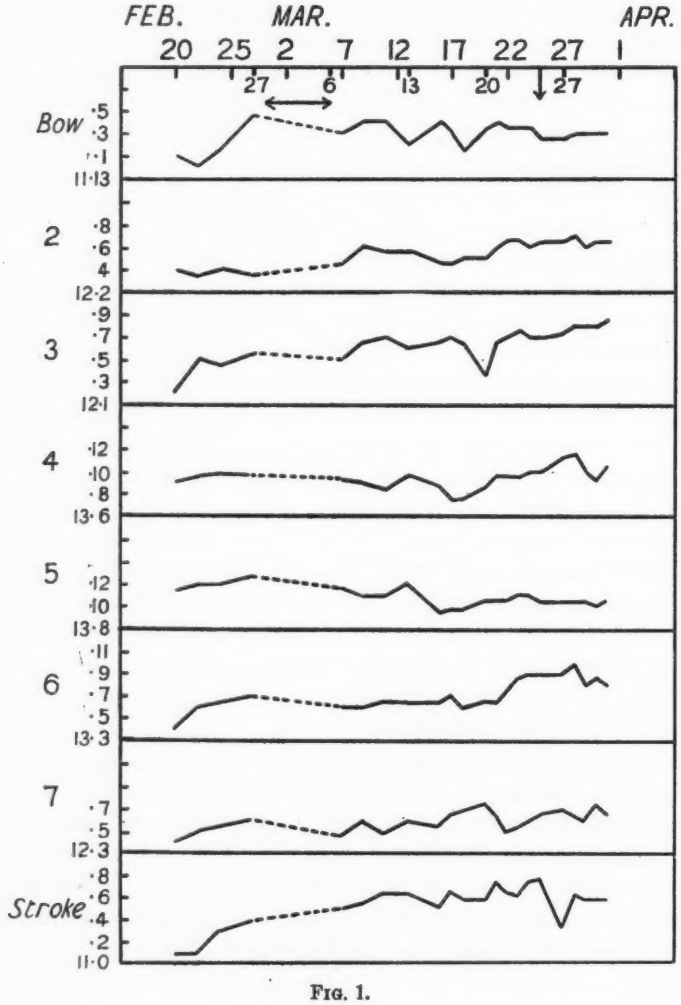


FIG. 1.

with general fatigue is undoubted. Schneider and Havens (10), who observed an increase in the haemoglobin content of the blood, after training, in the neighbourhood of 10 per cent., opined that staleness occurred as a result of a fall in this haemoglobin value, due to mild infection or excessive exertion. Be that as it may, the body-weight is as useful an indication as any we have of the onset of staleness. McKenzie (11) states that weight lost by a fit man as a result of

exercise should be replaced *in toto* in twenty-four hours, whereas this is not so if there be any degree of staleness present. Small fluctuations must not be taken too seriously; the normal loss of weight in the night is anything up to 1 lb.; and that the temperament of the athlete plays a large part in the question is shown by the weight charts of the members of the University Crew mentioned above. On the other hand a seemingly serious loss of weight may be rapidly regained and hence be of no serious significance.

The weight charts referred to are represented in Fig. 1; the records start soon after the constitution of the crew was finally settled, during practice on the Ouse at Ely; the interval shown by the dotted lines represent the period of rest between Ely and Henley, where the crew resumed practice on March 7; and the dates below the horizontal line are Mondays, no practice having taken place on Sundays. The vertical arrow marks the day of a full course row, from Putney to Mortlake, of some 20 minutes; the race was rowed on April 1.

At a glance, the fitness of the crew and absence of staleness, is seen by the general upward trend of all the graphs, with one exception—that of No. 5. This man happened to be President for the year; and it would seem not unlikely that the responsibility and added anxiety caused by the holding of this office, during an already anxious time, could account for the difference between his weight chart and those of the rest of the crew. Another noteworthy point is the almost general fall in weight during the days of rest shown by the falling dotted line. This is interesting in two ways: first, as showing that the two members of the crew who, as it happened, were most likely to be feeling the strain of intensive exercise—namely, 2 and stroke—definitely benefited by the rest; and, secondly, as showing that fit men taking strenuous exercise need that exercise continuously in order to preserve their body-weight constant or steadily rising.

The last point of interest on the charts is the effect of the full-course row on March 25—the last before the race. The heavy men in the middle of the boat, and even the lighter men towards the bows, though doing all the heavy work of propelling the boat, were so constituted mentally that they were able, without undue worrying, simply to give themselves up to the task of rowing their hardest from beginning to end; the result being that since they were fit men there is no loss of weight recorded after the row and a day's rest, and even in some cases there is a net gain. On the other hand, stroke—temperamental, 'highly-strung', of a worrying disposition, entrusted with the most important position in the boat, and upon whom depends so largely the excellence of the trial—though doing less actual work in foot-pounds than any other member of the crew, shows an immediate fall in weight of over 4 lb., only partially regained three days afterwards, and never completely regained. The charts are a remarkable commentary upon the influence of temperament on the fluctuations of body-weight during training.

Case History.

In this section will be given the full 'case-history', extending over five years, of an individual (the writer) indulging in regular strenuous exercise—that of rowing—including the period of training for the University Boat Race.

First Examination, Feb. 26, 1922. The subject, aged $23\frac{6}{12}$, had already rowed in college crews for three years. Weight 12 st. 13 lb. Height 6 ft. $0\frac{1}{2}$ in. Stem length 3 ft. $0\frac{1}{2}$ in.

The pulse was regular, though variable with excitement, of good volume, 64 per min. standing, 72 lying. The blood-pressure was 134/84 standing, 142–134/70 lying, 144/84 lying after exercise. The apex-beat was 4 in. from the mid-line in the 4th space, when standing; $4\frac{3}{4}$ in. and $4\frac{7}{8}$ in. from the mid-line in the 5th and 6th spaces respectively when lying. After exercise, lying, it was $4\frac{1}{8}$ in. from the mid-line in the 5th space. The first sound was clear, not very well sustained, but low-pitched; the second was rather muffled, reduplicated at the pulmonary base, but not accentuated at the aortic base. After 70 seconds of dumb-bell exercise the pulse-rate in 12 successive quarter-minutes was 96, 93, 81, 72, 72, 72, 66, 69, 75, 78, 78, 78. The movements of the chest were good and the lungs gave no sign of abnormality. The circumference was $36\frac{1}{4}$ in. in expiration, and the vital capacity 4410 c.c.

Second examination, March 25, 1922. This was made 2 hours after hard rowing exercise lasting $1\frac{1}{2}$ hours. The pulse was full in volume, regular, 112 per min. The blood-pressure was 130/78. The apex-beat, standing, was $4\frac{1}{4}$ in. from the mid-line in the 4th space, and lying, 4 in. from the mid-line in the 5th space. After exercise, lying, it was $4\frac{1}{2}$ in. from the mid-line in the 4th space.

Third examination, April 7, 1922. Made after a very hard day's exercise. The pulse was of good volume and variable rate, in the neighbourhood of 80 per min. The blood-pressure was 114/82. The apex-beat was $3\frac{1}{2}$ in. from the mid-line, in the 4th space, when standing; $4\frac{3}{8}$ in. from the mid-line, in the 4th space, when lying; and 4 in. from the mid-line in the 4th space, when lying after exercise.

On April 25, 1922, the subject rowed a long trial of 16 min. while not in strict training; no ill effects were observed.

Fourth examination, Oct. 17, 1922. The subject complained of discomfort under the left costal margin during the past three to four months; this was not present after food. There was no 'indigestion'; he had vomited once only, at night. There were no 'heart symptoms'.

The pulse was variable, in the neighbourhood of 84 per min. The blood-pressure was 130/88; the apex-beat, standing, was $3\frac{1}{2}$ in. from the mid-line in 4th space, and, lying, $4\frac{3}{4}$ in. from the mid-line in the 4th space. The heart sounds were good, low-pitched, and clear.

Fifth examination, Feb. 8, 1923. The subject was now in practice for the University Boat Race, though not in strict training. The pulse was regular, 68 per min.; the blood-pressure 138/88. The apex-beat, when standing, was $4\frac{3}{8}$ in. from the mid-line in the 4th space; when lying, it was 5 in. from the mid-line in the 4th space; and when lying after exercise, $4\frac{1}{2}$ in. from the mid-line in the 4th space. The heart sounds were clear, and were not those of a marked hypertrophy.

The 40 mm. U-tube test was applied at this stage (see section on The Assessment of Physical Fitness), and the figures were $6\frac{1}{2}/7$, $6\frac{1}{2}$, 6, 6, 6, 6, 6, $6\frac{1}{2}$.

Sixth examination, Jan. 18, 1925. The subject was now aged $26\frac{5}{12}$. He had gone down from Cambridge in April 1923, and had only rowed very occasionally since that date. The heart apex-beat was $4\frac{1}{2}$ in. from the mid-line in the 4th space.

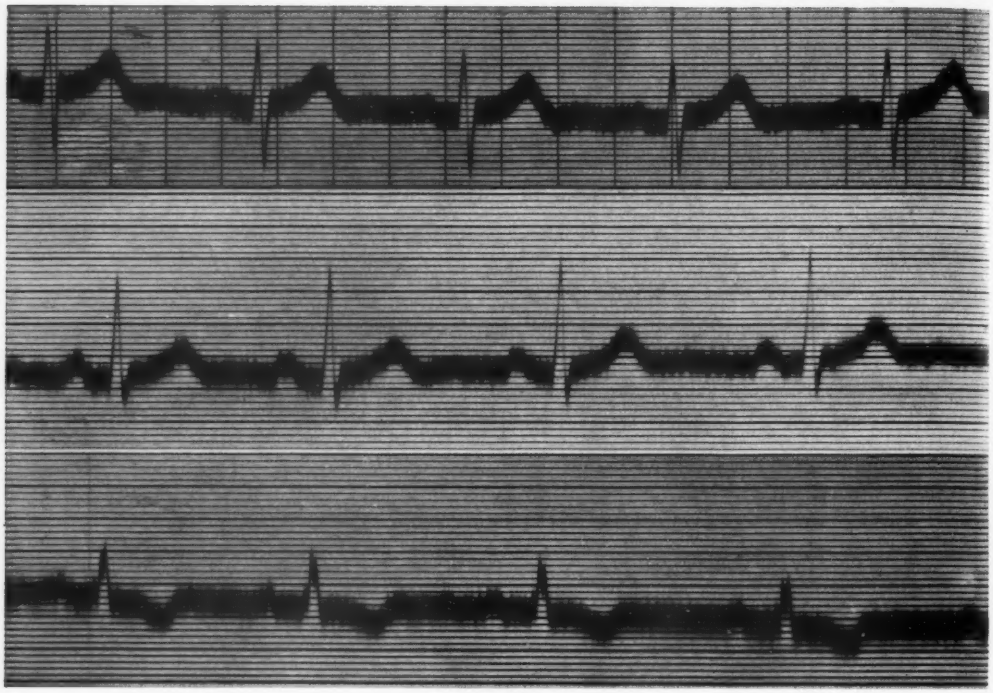


FIG. 2

Seventh examination, April 1927. No rowing was now being indulged in, but the subject was leading an ordinary, fairly active life. The pulse was regular, rate 64 per min., and of good volume. The blood-pressure was 120/80. The apex-beat was, when standing, 3¼ in. from the mid-line in the fifth space; when lying, it was 4½ in. from the mid-line in the 5th space. The heart sounds were clear, the first sound at the apex being low-toned and 'muscular' in nature; the pulmonary second sound was louder than the aortic second sound.

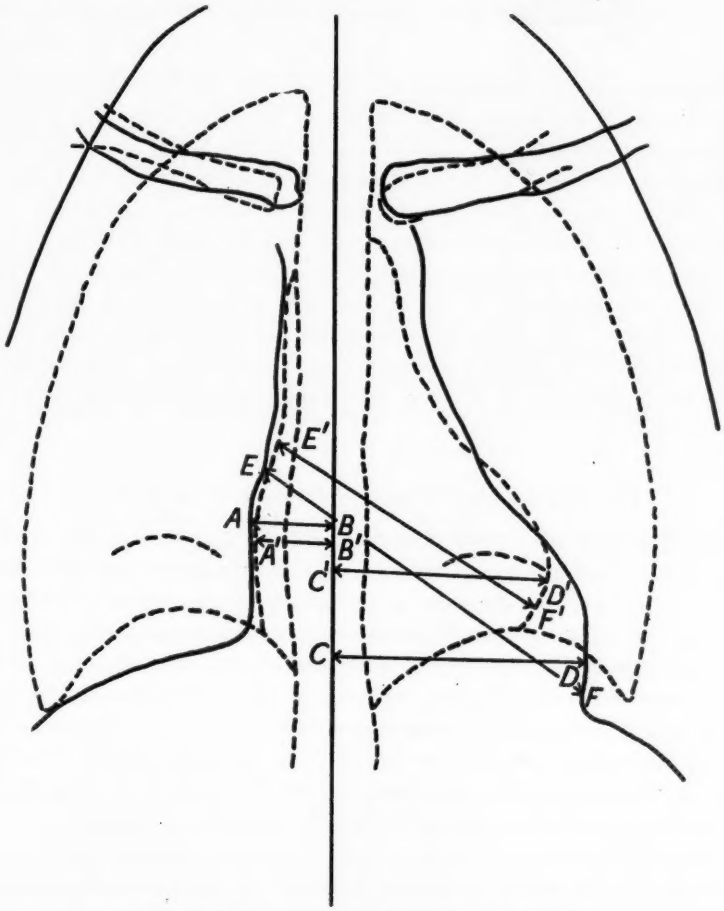


FIG. 3. Orthodiagram superimposed on a skiagram.

Three further examinations of the heart were made—by electrocardiograph, orthodiagram, and X-ray. The electrocardiographic curves reproduced on Pl. 17, Fig. 2, are normal, and do not even show a left-sided ventricular preponderance; the inversion of the T-wave in Lead 3 is of no significance.

The X-ray shadow and the orthodiagram were traced out, superimposed, and then mathematically reduced; the result is shown in Fig. 3, and is worthy of notice on account of its demonstration of the uselessness of X-rays as a

guide to the size of the heart. It will be seen that the outline of the skiagram falls well outside that of the orthodiagram, and conclusions drawn from the former would be erroneous; the actual measurements of both are given below and compared with the normals as given by Vaquez and Bordet.

	X-ray.	Ortho.	'Max. normal'.
Horizontal (AB + CD and A′B′ + C′D′)	15·4 cm.	13·2 cm.	13·2 cm.
Longitudinal (EF and E′F′)	18·1 cm.	14·2 cm.	13·8 cm.

Comments on the case-history will be made in the following section; one point—the size of the heart—will, however, be discussed here. The position of the apex-beat is admittedly a guide to the size of the heart; and while it is to be regretted that there is no record of its position before rowing was commenced at all, yet the figures given would certainly be abnormal for a man leading a sedentary life. Here is given definite proof that the heart is not only enlarged as a result of violent exercise, but that its size varies according to the demands made upon it; also, that by all clinical and subjective signs, the heart is perfectly healthy. The only conclusion which can reasonably be drawn is that the figures given support the contention that physiological enlargement of a healthy heart may occur as a result of strenuous physical exercise over a prolonged period.

The After-Effects of Exercise—Immediate and Remote.

The immediate after-effects of exercise differ in degree only, and not in kind, in the trained and the untrained man, and they may be summarized thus: there is an increase in pulse-rate, an increase in depth and rate of respiration, a rise of temperature and blood-pressure, and an increase in the metabolic-rate. Bainbridge summarizes the general difference between the effects on a trained and an untrained man by saying that, in the former, the pulse-rate is less, the blood-pressure lower, and the output per minute smaller. The last is an interesting observation, and must be explained by the higher degree of efficiency reached by the musculature after training, and the changes in such things as the coefficient of utilization and the carbon dioxide dissociation curve.

The pulse-rate always rises as a result of strenuous exercise, the rise in rate depending upon the degree of fitness, the nature of the work, and external conditions. The return to a slower rate—it may be to normal, or it may be to a lower level than this—is of considerable importance, and is dependent upon the state of training, as has been described. In an unfit man, and even rarely in a trained subject, temporary irregularity may follow upon strenuous exertion, but this is unusual.

The depth and rate of respiration are both increased during and after strenuous exercise. Only when the hydrogen-ion concentration of the blood and tissues has been reduced to normal again does the respiratory centre reduce the ventilation of the lungs to the previous resting level; until such a state is

reached, ventilation is above normal. In this connexion it has been stated that a well-trained oarsmen in a race adjusts his rate of respiration to his stroke—meaning, presumably, that the one is synchronous with the other. With this the writer cannot agree, having been unable to confirm the statement; indeed, if one considers the variations in the rate of striking over a long course, and the most probable rates of respiration at different points of the course, the likelihood of the occurrence of such a correspondence as is suggested would seem, on examination of the figures, to be remote.

The blood-pressure figures after exercise show a definite parallelism to those of the pulse-rate. The rise depends upon the degree of fitness, and the severity and type of the exercise. With regard to the last factor, it is found that the rise is more marked if the chest is fixed during exercise than if the exercise allows free play of the thoracic muscles. It is greatest after a short period of very severe exercise and falls rapidly, the rapidity here being probably due to dilatation of the cutaneous blood-vessels.

After due precaution had been taken to eliminate as far as possible any error due to mental effect on the subjects, Cooke and Pembrey (12) found a mean resting value of 113 mm. Hg., with a maximum of 132 and a minimum of 87 (16 observations upon 8 men). In the same experiment, the following figures were obtained for the systolic blood-pressure before and after exercise:

	Rest.	After Exercise.
(*a*)	132	202
(*b*)	109	170
(*c*)	97	134
(*d*)	112	190

The subsequent fall, like that of the pulse-rate, is often to a temporary value below the previous resting level.

The effect on the heart has been fully dealt with in previous sections; only a few actual examples will be quoted here. The physiological enlargement, described as occurring on taking exercise, depends again upon the nature of the exercise—if only a small number of muscles are used there will probably be no effect on the size of the heart.

The age of the subject is an important factor in this question, young people showing much more tendency towards enlargement than older ones, always of course provided that the latter have not reached the stage of senility. Rivierè (13) examined the hearts of 40 schoolboys who were taken on a school holiday excursion of one week's duration, the exercise consisting of walks of 6 to 8 miles daily, with some climbing, sports, and football in their spare time. More than half showed cardiac enlargement after their return, which was to be expected; but 10 of them, all of them among the younger boys, still showed dilatation after two and a half months. This is a clear indication that the exercise had been excessive and the rest periods inadequate, since dilatation occurred in hearts not ready for the sudden strain put upon them, and recovery and diminution in size did not occur. Against this may be set the observations of Zuntz (14) on 32 physicians between the ages of 35 and 60 who made the ascent

of the Brocken under unfavourable weather conditions. Here, men whose circulation had become established by age, and who knew by experience at what pace to tackle a piece of strenuous exercise, showed no bad effects and no cardiac dilatation after the exercise was over.

Most interesting results were obtained by Savage (14) when he investigated the size of the hearts of competitors in a 25-mile Marathon race at Pittsburg. Of six men with 'small vertical' hearts, none finished; of those with medium-sized hearts, four out of eight finished; of those with large hearts four out of seven finished; and two men, with hearts described as 'very large', both finished. Eleven were re-examined a week after the race; the hearts of two of them were larger than before the race, and those of nine of them were smaller, showing that the temporary enlargement to provide for additional work does not persist, in healthy men, after the demand for it has ceased.

A rise in body temperature is the inevitable result of strenuous exercise; and the rise is proportional to the intensity of the work, modified by external conditions. It plays an important part in affecting the adjustments made by the body to deal with its new requirements when exercise is commenced, and in the normal individual there is an immediate response in the form of a rise in pulse-rate and an increase in pulmonary ventilation. Haldane (15) states that a rise in temperature increases the sensitiveness of the respiratory centre, and as a result the active stimulus (namely, the rise in hydrogen-ion concentration) acts with greater effect.

With regard to the extent of the rise during and immediately after exercise; Bainbridge (16) holds that it is unusual in fit men to record a temperature of over 38·5° C. (101.5° F.), though values as high as 40° C. and 40·5° C. (104° F. and 104·9° F.) have been recorded. It is worth noting that mouth temperatures are far too unreliable to be of any use in these experiments; for readings during exercise the best method is to take a continuous rectal temperature, if possible, and for those after the completion of exercise it should be taken either similarly, or in the urine.

The only other immediate effects of interest are those on the renal system and the metabolic rate (already dealt with in part). There is always a mild degree of kidney disturbance following excessive exercise, caused no doubt by the excretion of irritant metabolites. McKenzie (17), following the observation of Collier, found albumin to be present in the urine of 73 per cent. of players of basket-ball, and in 100 per cent. of Marathon runners, after the race. In many cases, blood was also found, indicating a higher degree of disturbance.

The metabolic rate remains raised for some considerable time after the cessation of muscular activity. Since we have seen the same persistence occurs in the pulse-rate, this phenomenon affords another instance of the proportion existing between the pulse-rate and oxygen consumption. It is also interesting to note, that an increased oxygen consumption under these circumstances is not accompanied by an increase in the pulmonary ventilation.

The remote effects of muscular exercise are, apart from the muscular

system itself, mainly upon the circulatory system. There is a tendency for the blood-pressure to be somewhat raised in the case of a man who in previous years has indulged in considerable athletic or other exertion, the rise above normal being in the neighbourhood of 15 mm. of mercury. Michell (18) made records of the pulse-rate of 1,200 Cambridge rowing men during each of their three years of residence; while giving the average pulse-rate of a young healthy non-athletic man as 67·5, he found that the figures obtained from the athletic subjects were: in the first year, 69; in the second, 64·5; and in the third, 56·8. The figures would indicate that athletic pursuits, before the reaction to them was complete, cause a rise in pulse-rate, but that as the individual becomes accustomed to them and training becomes more nearly complete, there is a progressive fall. This is, indeed, the case; moreover, the diminished rate is persistent long after all athletic pursuits have ceased, and in many cases throughout the remainder of the individual's life. For instance, a few years ago a famous Cambridge oar showed severe abdominal symptoms, with a pulse-rate of 60; medical men well acquainted with the condition of 'athletic bradycardia' were called in to the case, operation was decided upon, and a gangrenous appendix was removed. The pulse-rate had, in fact, increased by some 16 beats per minute above his normal.

The possibility of a permanent harmful effect of muscular exercise, especially competitive athletic exercise, upon the heart, has been the subject of discussion on many occasions, and although some years ago it was usual to conclude that this possibility was indeed a fact, the tendency amongst recent observers is to disagree with this idea. Quotations from two famous authorities, viewing the problem from different standpoints, will be apposite. Bainbridge (19) says: 'There is no direct evidence that, provided a man is physically sound and in good health, exercise, however severe, is ever harmful or followed by serious after effects'. And Allbutt gave it as his opinion that, 'the importance of muscular effort as a factor in cardiac injury has been much exaggerated. In the sound adult organism the effects of physical stress on the heart are promptly counteracted by equilibrating machinery'.

Morgan (14) came to the conclusion that no harm ensued from strenuous athletic exercise, after investigating the condition of members of the Oxford and Cambridge Boat Race crews between the years 1829 and 1869. There were 255 survivors: he communicated with 151 of these, and with the relatives of 39 who had died. In all, 7 spoke of themselves as 'injured' by their athletics, or were so described by their relatives, often with considerable reservation. On tabulating these men with reference to expectation of life, he found that this was 42 years; Parr's English Life Insurance Tables place the expectation of a man of 20 at 40 years. In investigating the 39 deaths he found as causes: in 11 cases, fever; in 7 cases, consumption; in 2 cases, some other form of chest complaint; in 6 cases, accident; in 3 cases, heart disease; in 1 case, Bright's disease; and in 8 cases, various causes not connected with athletics. Nearly all the cases dead of consumption showed a strong personal or family history; and

there were no sudden deaths or rapidly fatal heart cases. The mortality amongst these men from disease of the circulatory apparatus and from consumption was about the average as disclosed by the Registrar General's report; and an important consideration is that in those days men rowed without medical examination, the unfit being weeded out by the more costly elimination of the oar.

Similar results were obtained by Meylan (14) in investigating longevity amongst Harvard oarsmen, who found an average increase per man of 1·6 years as compared with the figures in the Insurance Tables. The results were moreover modified by a number of deaths of men in their prime in the Civil War; allowing an average expectation to those who were so killed, the advantage becomes 5·39 years per man. Of 32 deaths amongst these oarsmen, two were due to heart disease, and in neither case was the disease attributed to rowing; two survivors believed that rowing had injured them, one claiming to have dyspepsia and the other an enlarged heart which, however, caused him no inconvenience whatsoever. These facts bear out the inevitable conclusion to be drawn from Morgan's observations, with the one difference that these latter men were medically examined and pronounced fit for boat-racing, and hence were, in a sense, 'selected lives'.

General Conclusions.

In reviewing the subject as a whole one cannot but be struck by the delicacy of the various mechanisms which operate in the human organism during and after indulgence in muscular effort, and even before the commencement of the effort. These mechanisms are as intricate as any in the body, but provide far more interest than most in their peculiar property of being capable of voluntary education, which increases their efficiency and thus increases the efficiency of the whole human machine.

Perhaps also enough has been said here to indicate the definite desirability of subjecting all those who intend to take part in strenuous athletic pursuits to a searching preliminary medical examination, and several subsequent 'overhauls'. This procedure would prevent any occurrence of organic injury as a result of the undoubted strain which such sports impose upon the participator. In this connexion, finally, the following conclusions may be drawn from what has been here set down: that no exercise, however strenuous, can permanently harm the healthy trained man; that, of two men in middle life, it is sometimes possible to tell the previously athletic from the previously non-athletic, by clinical methods; and that, the healthy heart is capable of physiological enlargement, again detectable by clinical means, in order to deal with a temporary extra amount of work, and further is capable of physiological diminution in size when the stimulus to this response is discontinued.

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OBSERVATIONS ON THE METABOLISM OF AMINO-ACIDS IN HEALTH AND DISEASE[1]

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Introduction.

Recent work by Mann (14) and others has excited renewed interest in the part played by the liver in protein metabolism. It is well known that proteins are broken down in the alimentary canal and absorbed as amino-acids and peptides. The blood of a fasting animal contains 5–7 mg. per cent. of amino-nitrogen. After a protein meal this rises to 10–20 mg. per cent. This increase represents only a fraction of the absorbed amino-acid, very little of which remains in the blood-stream. The greater part is taken up by the tissues, especially the liver and the muscles, which may contain 60–100 mg. per cent. of amino-nitrogen after a protein meal, the fasting content being 40–50 mg. per cent. The amino-acid is loosely attached to the tissues, apparently by adsorption. The nitrogenous moiety is rapidly converted into urea.

Until Mann's work was published, it remained a matter for controversy whether urea formation was localized in the liver or whether it could take place in other tissues. 'Present experimental results may be interpreted by stating that the most active centre of amino-acid transformation and of urea formation appears to be the liver, but that the localization of the function is not absolute and that these processes may also occur to some extent in other organs' (Van Slyke, 1920 (16)). Mann (14) has devised a technique whereby the liver may be completely removed in dogs. Animals can be kept alive for many hours after the operation. They lose the power to form urea, the blood-urea sinks to zero, and when large amounts of amino-acid are injected no urea is formed. The injected amino-acids are taken up by the muscles and the amino-nitrogen of the blood soon falls to normal. The evidence is clear that urea can be formed only by the liver. In other experiments the amount of liver tissue was reduced to 20 per cent. of the normal, and the function of this remnant was probably impaired by the operative procedures. Nevertheless urea formation was normal. Thus Mann's experiments show that although urea formation is confined to the liver, the liver has a very great reserve capacity.

Tests of liver function in man have been based on the study of amino-acids and urea in the blood or urine (Jastrowitz (11), Falk and Saxl (5), Frey (9),

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Cohen and Levin (3)). To investigate these tests I have carried out a number of experiments on normal people and on patients suffering from various diseases. These experiments show that there is no evidence that amino-acids are significantly increased in the blood in diseases of the liver, with the exception of acute yellow atrophy and similar conditions in which the cells of the liver undergo necrosis and autolysis. The increase is then due to the absorption of the autolysed tissue. My experiments also show that urea formation may sometimes be deficient in diseases of the liver, but that disturbance of urea formation occurs also in conditions which are not thought of as diseases of the liver, while in gross and obvious liver disease the formation of urea may be normal. It is the purpose of this paper to present these results in detail and to demonstrate the inapplicability of protein tests to the estimation of hepatic efficiency.

Method.

In studying the metabolism of amino-acids I have given glycine by mouth in doses of 50 grm. A 10–15 per cent. solution in water has a not unpleasant sweet taste. It can be flavoured with lemon juice. It not infrequently causes vomiting. The dose may then be reduced to 25 grm., though patients with catarrhal jaundice are usually unable to retain even this smaller dose. I have considered it out of the question to give glycine intravenously. Small amounts of 2·5 grm. have indeed been given in this way without harm by German workers, but these amounts are inadequate for the study of urea formation. When large doses of 50 grm. are injected in animals with liver disease, the animals not infrequently collapse and die. I have tried the oral administration of 50 grm. of casein and 250 grm. of raw liver. They are more nauseous than glycine and absorption is irregular.

The arrangement of the experiments was as follows. The patients received no food for fourteen hours before the test, and during it only water was given. Blood samples were taken before and at intervals after the ingestion of glycine. Amino-nitrogen, non-protein nitrogen, uric acid, and sugar were estimated by the methods of Folin (8), urea by the urease method. All estimations were made on whole blood. Results of a typical test in a normal man are charted in Fig. 1. After the ingestion of 50 grm. of glycine, the amino-nitrogen of the blood rises from a fasting level of about 7 mg. per cent. to about 12 mg. per cent. It reaches a peak in one to four hours, and falls to the fasting level in six to eight hours. The blood-urea rises later: the peak is reached in three to six hours and the level remains high at eight hours. Blood-sugar is unaffected or may rise a little.

Fasting Amino-acid.

I have determined the fasting amino-nitrogen in 31 conditions other than disease of the liver. The average value was 6·3 mg. per cent. Twenty-seven of the cases lay between 5·4 and 7·4 mg. per cent. Low values were found in an

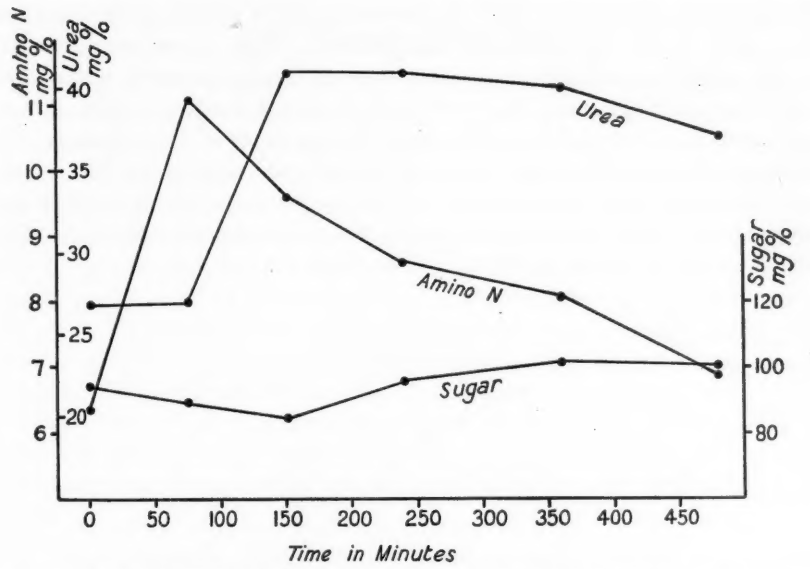


FIG. 1. Blood-urea, amino-nitrogen and sugar in normal subject after 50 grm. of glycine.

TABLE I. *Fasting Amino-nitrogen.*

Liver Diseases.		Other Conditions.	
Hypertrophic cirrhosis	5·0	Myxoedema	5·0
Malignant disease of liver	5·7	Neurosis	5·1
Catarrhal jaundice	6·0	Lead poisoning	5·4
Obstructive jaundice	6·0	Chronic bronchitis	5·4
Portal cirrhosis	6·3	Hyperthyroidism	5·4
Portal cirrhosis	6·5	Diabetes mellitus	5·6
Haemolytic jaundice	6·8	Sciatica	5·6
Catarrhal jaundice	7·4	Encephalitis lethargica	5·6
Banti's disease	7·5	Bronchiectasis	5·7
Obstructive jaundice	7·7	Hyperpiesia	5·7
Cardiac liver	8·0	Sciatica	5·9
Acute hepatic insufficiency	8·6	Sciatica	5·9
		Gout	5·9
		Subacute rheumatism	6·0
		Pyelitis	6·2
		Gastro-enteritis	6·2
		Addison's disease	6·3
		Normal student	6·4
		Convalescent pneumonia	6·5
		Duodenal ulcer	6·6
		Diabetes mellitus	6·7
		Chorea	6·7
		Contusional headache	6·7
		Exophthalmic goitre	6·7
		Chronic nephritis	6·9
		Gout	7·0
		Diabetes mellitus	7·0
		Acute nephritis	7·2
		Disseminated sclerosis	7·4
		Uraemia	7·7
		Leukaemia	8·8
Average	6·8	Average	6·3

untreated case of myxoedema, 5·0 mg. per cent., and in a nervous patient in whom no organic lesion was found, 5·1 mg. per cent. High values were found in a patient with uraemia, who had a blood-urea of 182 mg. per cent., amino-nitrogen 7·7 mg. per cent.; and in a case of leukaemia 8·8 mg. per cent. I have estimated the fasting amino-nitrogen in twelve cases of liver disease. The average value was 6·8 mg. per cent., and in ten of the cases it lay between 5·7 and 8·0 mg. per cent. A low value of 5·0 mg. per cent. was found in a case diagnosed as Hanot's cirrhosis, and a high value of 8·6 mg. per cent. in a patient who died in coma following cirrhosis of the liver.

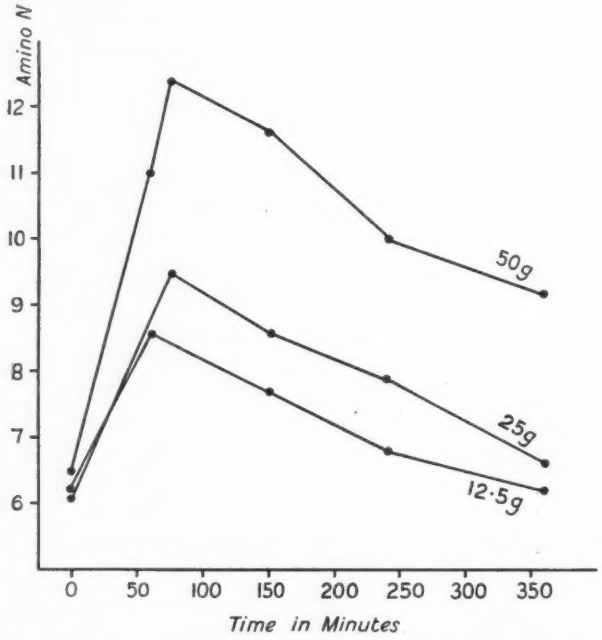


FIG. 2. Amino-nitrogen in blood after different doses of glycine.

These observations may be compared with the results of Greene, Sandiford, and Ross (15). They found that the amino-nitrogen of the blood varied between 4·8 and 7·8 mg. per cent., the average amount being 6·3 mg. This was found to be true in normal persons and in a series of more than 400 observations covering twenty different pathological conditions. They did not study the post-absorptive level, but they noted that the amino-nitrogen might be increased during digestion, or from the rapid autolysis of body tissue in leukaemia and acute yellow atrophy. They commented on the remarkable constancy with which the amino-nitrogen of the blood was kept within the above limits, and remarked that such disease conditions as diabetes, uraemia, exophthalmic goitre, or hepatic insufficiency were not exceptions to this rule. Similar results are reported by v. Falkenhausen (6) and by Feinblatt and Shapiro (7).

The Amino-nitrogen Curve.

In Fig. 2 I have shown the variations in the amino-nitrogen content of the blood after different doses of glycine. I have made only one curve after 12·5 grm. of glycine. The curve for 25 grm. is the average of four cases and the curve for 50 grm. is the average of thirteen cases. The amino-nitrogen begins to rise very soon after glycine has been taken. A definite rise occurs with 12·5 grm. of glycine. After 25 grm. the amino-nitrogen rises to about 10 mg. per cent., and after 50 grm. it rises to about 12 mg. per cent. I have not been able to push the dose beyond 50 grm. on account of vomiting, but it seems that there is an upper limit to the amino-nitrogen content of the blood, and that this limit is not exceeded however much glycine is taken. This limiting value is about 15 mg. per cent. The peak occurred at sixty minutes after 12·5 grm. of glycine. With the higher doses it came between the first and the fourth hour, the average time being 150 minutes. The larger the dose, the slower is the return to the fasting level, and when 50 grm. of glycine are given this may not be regained in eight hours.

TABLE II. *Post-absorptive Values of Amino-nitrogen.*

After 25 grm. of glycine:

Liver Diseases.		Other Conditions.	
Catarrhal jaundice	11·8	Sciatica	8·8
Haemolytic jaundice	10·1	Colitis	8·7
Portal cirrhosis	9·3	Gout	9·3
		Plumbism	11·1
Average	10·4	Average	9·5

After 50 grm. of glycine:

Liver Diseases.		Other Conditions.	
Cardiac liver	9·8	Convalescent nephritis	12·0
Obstructive jaundice	9·5	Convalescent pneumonia	10·0
Malignant liver	13·3	Disseminated sclerosis	12·9
Hanot's cirrhosis	10·8	Uraemia	15·2
Banti's disease	13·3	Diabetes mellitus	11·8
Portal cirrhosis	9·3	" "	10·3
		" "	11·1
		Myxoedema	17·9
		Exophthalmic goitre	11·1
		Hyperpiesia	14·8
		Leukaemia	12·3
		Gout	9·8
		Normal student	11·1
Average	10·9	Average	12·4

I have made over thirty of these amino-nitrogen curves and found the results surprisingly constant in health and disease (see Table II). After casein and liver the curves were not so smooth and absorption seemed to be irregular, but there were no essential differences. Seven curves were made after the ingestion of 25 grm. of glycine. Three of these were in liver disease and the average maximum post-absorptive amino-nitrogen was 10·4 mg. per cent.; four were from patients not suffering from liver disease, and the average maximum

was 9·5 mg. per cent. Nineteen curves were made after the ingestion of 50 grm. of glycine. Thirteen of these were in patients not suffering from liver disease, and the average maximum was 12·4 mg. per cent.; in six cases of liver disease it was 10·9 mg. per cent. The highest post-absorptive value in liver disease was 13·3 mg. per cent. in a patient suffering from secondary melanotic sarcoma of the liver with very great enlargement. This was exceeded by 14·8 mg. per cent. in a case of hyperpiesia, 15·2 mg. per cent. in a case of uraemia and 17·9 mg. per cent. in a case of myxoedema.

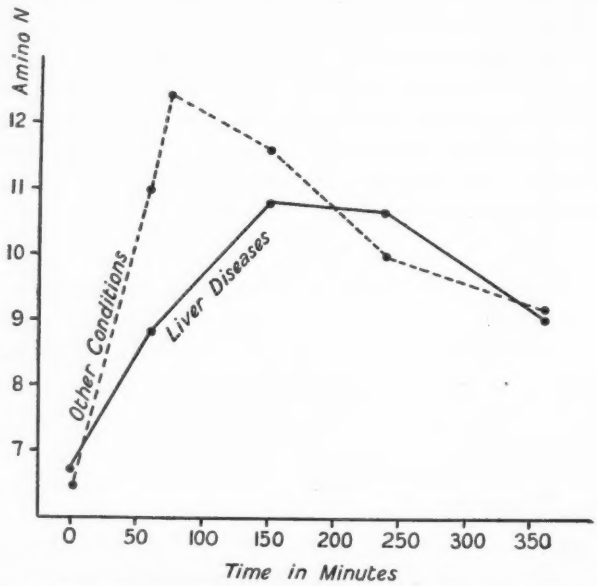


FIG. 3. Composite curve of amino-nitrogen in blood after 50 grm. of glycine in 6 cases of liver disease and 13 patients suffering from other conditions.

For convenience of presentation I have constructed composite curves of the variation of amino-nitrogen in the blood after the ingestion of 50 grm. of glycine in these two groups of cases. Fig. 3 shows that the values for the amino-nitrogen of the blood ran slightly lower in the patients in whom the liver was diseased. It is believed that the amino-acids become attached to the tissues by a purely physical process of adsorption. In five of the six cases of liver disease the liver was palpably enlarged. It is therefore possible that a larger surface was offered for adsorption, and that the lower amino-nitrogen curve in diseases of the liver is to be explained on mechanical grounds.

Blood-urea.

The variations in the blood-urea after the ingestion of different doses of glycine are shown in Figure 4. These are typical curves from three different normal men. The blood-urea shows such great differences in different subjects,

in health as well as in disease, that it is difficult to put results on a basis on which they can be compared. The actual increase in the blood-urea is not a good measure of the amount of urea formed, as no account is then taken of the rate of excretion of urea during the test. The fasting level of urea in the blood may be considered a function of the rate of formation of urea in the body and the rate of excretion of urea by the kidney. Cohen and Levin (3) therefore used the fasting level of urea in the blood as a base-line, and they considered that the percentage increment of the blood-urea above this level after the ingestion of protein was a measure of the urea formed. Thus if the fasting blood-urea was 25 mg. and it rose to 40 mg., the percentage increment would be 60 per cent. They found that the blood-urea increased at least 50 per cent. after a meal of 50 grm. of protein.

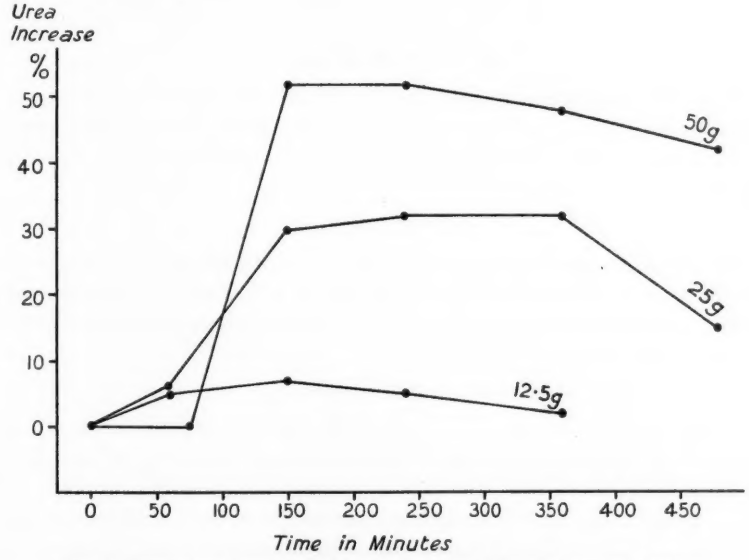


FIG. 4. Percentage increase of blood-urea after different doses of glycine.

This formula is quite empirical, and comparable results are only obtained if the fasting blood-urea is within the usual limits and the renal activity is normal. It is obvious that the formula must break down if the fasting blood-urea is much above normal.

In most of the cases studied the blood-urea and the renal function were normal. I have therefore expressed the increases in blood-urea as percentage increments above the fasting level. There is quite a definite increase in the blood-urea after the ingestion of 12·5 grm. of glycine. After 25 grm. of glycine the increase in healthy subjects is not less than 30 per cent., and after 50 grm. not less than 50 per cent. The increase is, however, very variable, ranging from 50 to 113 per cent. (Table III). The blood-urea rarely rises much in the first hour, and a big increase usually does not occur till the fourth hour. The peak of urea

formation is usually at the sixth hour, and values are still high at the eighth hour, though the curve is then falling. Thus there is a definite lag between the increase of amino-acid in the blood and the formation of urea, the peaks of the curves being usually separated by an interval of two to four hours.

TABLE III. *Changes in Blood-urea in Normal Subjects.*

Time.	0′.	240′.		360′.	
Dose of Glycine.	Urea.	Urea.	Increase.	Urea.	Increase.
12·5 grm.	40	42	+5%	41	+2%
25 grm.	20	32	+60%	–	–
	34	45	+32%	45	+32%
	29	40	+38%	42	+45%
50 grm.	15	32	+113%	–	–
	28	44	+57%	48	+71%
	27	41	+52%	40	+48%

Non-protein Nitrogen.

When the non-protein nitrogen was estimated in these experiments, it was found to undergo changes which reflected the changes in the amino-nitrogen and urea nitrogen. I shall therefore make no further reference to the non-protein nitrogen.

Blood-sugar.

The level of sugar in the blood usually rises a little after the ingestion of glycine. This is true not only in health, but also in diseases of the liver and in diabetes. I am reserving a full discussion of the blood-sugar changes for a later communication.

Liver Disease.

I have already discussed the fasting and post-absorptive levels of amino-nitrogen in the blood in liver disease and have shown that they are not different from those found in health. In Table IV I have tabulated the figures obtained from the study of the blood-urea in these cases. There were nine proved cases of liver disease. Yet in only two—a portal cirrhosis and a metastatic melanotic sarcoma of the liver—was the formation of urea defective. In three others—catarrhal jaundice, Hanot's cirrhosis, and Banti's disease—there was slight delay.

TABLE IV. *Urea formation in Liver Disease.*

Dose of Glycine.	Disease.	0′. Urea.	240′. Urea.	Increase.	360′. Urea.	Increase.
25 grm.	Catarrhal jaundice	25	28	12%	35	40%
25 grm.	Acholuric jaundice	25	43	72%	35	40%
25 grm.	Portal cirrhosis	34	34	Nil	35	3%
50 grm.	Obstructive jaundice	33	63	90%	65	96%
50 grm.	Obstructive jaundice	23	57	148%	51	122%
50 grm.	Malignant liver	32	42	31%	42	31%
50 grm.	Hanot's cirrhosis	22	31	41%	37	68%
50 grm.	Portal cirrhosis	25	38	52%	45	80%
50 grm.	Banti's disease	29	42	45%	47	62%

From these results I conclude that urea formation is one of the last functions to fail in hepatic disease. That it may ultimately fail is shown by one of the cases of portal cirrhosis. This was a woman who had been admitted to hospital about twelve months before on account of abdominal discomfort and jaundice. A diagnosis of cholelithiasis was made, but at operation the gall-bladder was normal and the liver showed hobnail cirrhosis. Jaundice persisted with slight fluctuations, and about two months before the test was performed the patient developed ascites which rapidly recurred in spite of tapping. The amino-nitrogen curve was normal but the blood-urea showed no increase after 25 grm. of glycine. The blood-sugar, as sometimes happens in advanced liver disease, was low, 75 mg. per cent. (fig. 5).

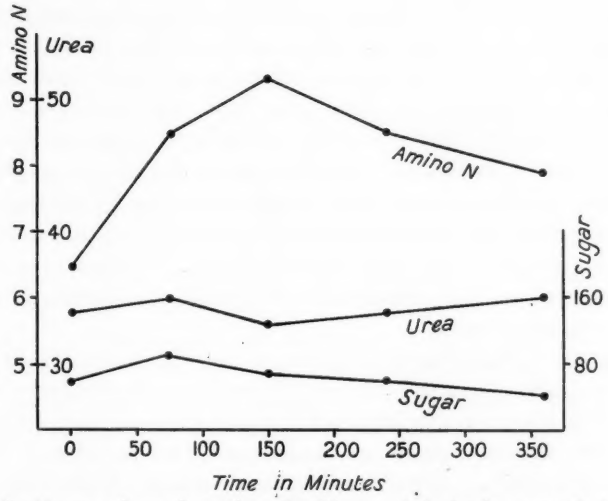


FIG. 5. Absence of urea formation after 25 grm. of glycine in a case of advanced liver disease.

Cardio-vascular and Renal Disease.

In chronic passive venous congestion of the liver the protein metabolism appears to be normal. I gave 50 grm. of glycine to a youth with chronic rheumatic heart disease and heart failure, whose liver had been enlarged below the umbilicus for more than twelve months. The amino-nitrogen, which was 8 mg. per cent. in the fasting blood, rose to 9·8 mg. per cent. The blood-urea, which was 43 mg., rose to 68 mg. at the fourth hour and 80 mg. at the sixth hour, increases of 58 per cent. and 86 per cent. respectively.

The other cardio-renal disorders studied were hyperpiesia and uraemia. In the patient with hyperpiesia the systolic blood-pressure varied from 150 to 210 mm. of mercury. The amino-nitrogen rose from a fasting level of 5·7 mg. per cent. to 14·8 mg. per cent. 150 min. after the ingestion of 50 grm. of glycine. The blood-urea rose from 47 mg. to 65 mg. at the fourth hour and 68 mg. at the sixth hour, increases of 38 per cent. and 45 per cent. respectively. Thus the amino-nitrogen

curve was high and urea formation was defective. In the uraemic patient the fasting amino-nitrogen was a little high, 7·7 mg. per cent. It rose to 15·2 mg. per cent. 150 min. after 50 grm. of glycine. The blood-urea rose from 186 mg. to 254 mg. at the fourth hour. The experiment was not continued longer as the patient was very weak. The urea increment was only 37 per cent. of the fasting value, so that urea formation was below normal on the percentage basis.

Diabetes Mellitus.

In spite of earlier statements to the contrary, it is now agreed that the amino-nitrogen of the blood is within normal limits in diabetes mellitus. The amount excreted in the urine may be slightly increased by the polyuria. The injection of insulin is followed by a fall in the amino-nitrogen of the blood and urine, both in healthy subjects and in diabetics. Wiechmann and Dominick (18) found that when 2·5 grm. of glycine were injected intravenously into diabetics, the amino-nitrogen took longer to return to the original level than in normal subjects. If insulin was injected before the glycine, the original level was reached more rapidly than in the normal. In the three cases of diabetes mellitus I have studied, the amino-nitrogen curve after 50 grm. of glycine by mouth was normal. In two of the patients the experiment was repeated with the addition of insulin. There was no change in the amino-nitrogen curve. It seems that when large amounts of glycine are being absorbed the effect of insulin on the amino-nitrogen of the blood is inappreciable.

I have summarized the urea figures in these patients in Table V. Urea formation was defective in two of them. Case II had had diabetes for eighteen months. After 50 grm. of glycine the blood-urea increased only 46 per cent. by the sixth hour. The experiment was repeated with the addition of 25 units of insulin subcutaneously. Urea formation was unchanged, the increase being 45 per cent. at the sixth hour. Case III was a recent diabetic who had had symptoms only three weeks. After 50 grm. of glycine the blood-urea only increased 25 per cent. at the sixth hour. I repeated the test with the addition of 20 units of insulin. The blood-urea at the sixth hour was now increased by 48 per cent.

TABLE V. *Urea Formation in Diabetes Mellitus.*

	0′.	240′.		360′.	
	Urea.	Urea.	Increase.	Urea.	Increase.
Case I.					
50 grm. glycine	24	35	+46%	47	+92%
Case II.					
(*a*) 50 grm. glycine	28	35	+25%	35	+25%
(*b*) 50 grm. glycine + 20 units insulin	29	36	+24%	43	+48%
Case III.					
(*a*) 50 grm. glycine	28	40	+43%	41	+46%
(*b*) 50 grm. glycine + 25 units insulin	31	42	+35%	45	+45%

These experiments and others which I have performed show that the blood-urea in diabetic patients does not increase to the usual extent after the ingestion

of glycine. None of these patients had acidosis, and it would appear that the phenomenon is not a temporary one, as it has been observed over a period of months in the same patient. On the data at present available I cannot say whether there is a definite disability in metabolizing amino-acids in diabetes mellitus. This question of the protein metabolism in diabetes mellitus is of great importance, and I propose to discuss it more fully in a subsequent paper.

Other Metabolic Disorders.

In a patient with exophthalmic goitre the amino-nitrogen rose from a fasting level of 6·7 mg. to 11·1 mg. four hours after the ingestion of 50 grm. of glycine. The urea increase was 45 per cent. at the fourth hour and 50 per cent. at the sixth hour. In an untreated case of myxoedema the amino-nitrogen rose from a fasting level of 5 mg. to a post-absorptive peak value of 17·9 mg. 75 min. after the ingestion of 50 grm. of glycine. This is the highest amino-nitrogen I have found. The blood-urea was increased 30 per cent. at the fourth hour and 67 per cent. at the sixth hour. I was unable to follow the effect of treatment on the amino-nitrogen curve, as the patient vomited copiously when the test was repeated. In a patient recovering from an acute attack of gout the fasting uric acid was 5·1 mg., the amino-nitrogen 5·9 mg. per cent. The amino-nitrogen reached a value of 9·8 mg. 150 min. after the ingestion of 50 grm. of glycine. The blood-urea increased 36 per cent. at the fourth hour and 58 per cent. at the sixth hour. Thus in these three diseases—exophthalmic goitre, myxoedema, and gout—urea formation was within normal limits, but there was some delay, an increase of 50 per cent. in no case being reached before the sixth hour.

Leukaemia.

I have studied one patient with chronic myeloid leukaemia. The white cells numbered 95,000 per cubic mm. The fasting amino-nitrogen was high, 8·8 mg. per cent., but after 50 grm. of glycine it only rose to 12·3 mg. The blood-urea rose from 32 mg. to 53 mg., an increase of 66 per cent. Thus urea formation was normal in this disease, and though the fasting amino-nitrogen was high there was no disturbance in the storage of ingested amino-acid.

Discussion.

In the introduction to this paper I have given a short review of experimental work on animals which shows that amino-acids are taken up not only by the liver but also by the other tissues of the body, especially the muscles. Even if the liver is completely removed, injected amino-acid disappears rapidly from the blood-stream and the level returns to normal. It seems unlikely, therefore, that any gross disturbance in the amino-nitrogen of the blood should occur in liver disease in man. In my experiments on patients with liver disease a high fasting

amino-nitrogen was found only in a patient dying from acute hepatic insufficiency. A high amino-nitrogen is not infrequent in agonal conditions, especially in acute yellow atrophy of the liver, when large numbers of cells are undergoing autolysis in the body. It has long been known that crystals of leucine and tyrosine may appear in the urine in acute yellow atrophy of the liver. They arise from the disintegration of liver-cells and this isolated phenomenon has little bearing on the general question of the amino-nitrogen metabolism.

Yet the occasional appearance of large amounts of amino-acid in the blood and urine in acute yellow atrophy has been misconstrued into the belief that this is a usual finding in other diseases of the liver. There is no evidence that the amino-acids in the blood or the urine are increased in other diseases of the liver. Levene and Van Slyke (quoted by Bauman (2)) found no increase of amino-acids in the urine of animals poisoned with chloroform or phosphorus, even when the liver was extensively degenerated. In two cases of human cirrhosis the amino-acids of the urine were not increased. There was no increase in the amino-acid in the blood or urine in toxaemia of pregnancy, though the urine urea was diminished. 'With the possible exception of acute yellow atrophy, an increase of amino-acids in the blood or urine is an infrequent occurrence in hepatic disease' (Bauman). I have also shown that when the organism is subjected to strain by the intake of large amounts of preformed amino-acid, the post-absorptive level of amino-nitrogen in the blood is no higher in liver disease than in health, and the excess amino-acid disappears from the blood at the same rate. Similar results have been reported by v. Falkenhausen (6). Tests based on the estimation of amino-nitrogen in blood and urine would therefore appear to have no value in the study of liver function.

The fasting and post-absorptive levels of amino-nitrogen are a little raised in uraemia. This may be the result of renal insufficiency, though it is not commensurate with the increase in the other non-protein nitrogenous constituents of the blood. A slight increase in the fasting amino-nitrogen has also been described in hyperpiesia. I did not find this in my cases, though in one patient with hyperpiesia the post-absorptive level was rather high. It is well known that the uric acid of the blood is increased in hyperpiesia.

In my experiments the fasting and post-absorptive values of the amino-nitrogen of the blood were normal in hyperthyroidism. The highest post-absorptive value for amino-nitrogen I have recorded was in an untreated case of myxoedema. However, Liebeschuetz-Plaut and Schadow (12) studied several patients with this disease and found normal fasting and post-absorptive values for amino-nitrogen. It is generally believed that the rise in metabolism which occurs after a protein meal is due to the circulation of increased amounts of amino-acid in the blood-stream. It can be duplicated by the injection of glycine. Liebeschuetz-Plaut and Schadow found that not only did the amino-nitrogen of the blood increase to the usual degree after protein meals in patients with myxoedema, but the specific dynamic action of the proteins also was normal. They studied another group of cases of obesity which they attributed to pituitary

disease. In these patients they found that the amino-acids in the blood did not increase or increased only very little after a big protein meal, and the specific dynamic action of the protein was diminished or absent.

The amino-nitrogen of the blood is always raised in leukaemia with high leucocyte counts. It is well known that uric acid is also present in large amounts in leukaemic blood. Both these substances are believed to be increased as a result of the breakdown of white cells and a similar increase of amino-nitrogen occurs whenever large numbers of leucocytes are being broken down. Loeper, Decourt, and Lesure (13) have shown that amino-acid is formed in cellular exudates and may be absorbed from these and cause a rise in the amino-nitrogen of the blood. They found that during a pneumonia the amino-nitrogen of the blood was slightly raised—7·5 to 8 mg. per cent.—and at the crisis it rose to 9·7 mg. per cent., maintaining this value for five days afterwards.

Donath and Heilig (4), and Weichmann and Horster (19) have studied the behaviour of the amino-acid of the blood in fever. In fevers caused by bacterial infection and malaria the amino-nitrogen of the blood is unchanged. When fever is provoked by the injection of foreign protein there is a transient rise in the amino-nitrogen of the blood at the height of the febrile reaction. The amino-nitrogen may rise after very small doses of foreign protein, and it is therefore most likely that it is derived from the breakdown of body protein. Wells (17), in reviewing the chemical aspects of anaphylaxis, states that there is evidence of an increased destruction of protein, but the increase in amino-acids, presumably derived from proteolysis in the sensitized individual, is not large enough to be significant. However, in anaphylaxis in guinea-pigs, as well as after peptone poisoning, there is a considerable increase in non-coagulable and urea nitrogen in the blood, as well as a slight increase in creatinine and amino-nitrogen. It is not known whether this comes from the tissues or the antigen-antibody reaction in the blood, although the former seems more probable. Barber and Oriel (1) have recently published the results of a chemical investigation of asthma and allied conditions of hypersensitiveness. They found that in the quiescent periods of the disease the amino-nitrogen of the blood was normal or slightly raised, but that during the paroxysms it might be increased twofold. They attributed this to an underlying disorder of the liver. I have shown, however, that the amino-nitrogen metabolism is normal in liver disease. The changes in the blood in the asthmatic paroxysm are comparable with those in protein shock and anaphylaxis, and probably result from the breakdown of body protein in the sensitized organism.

Although the formation of urea from amino-acids is confined to the liver, this function is not applicable as a test of 'hepatic efficiency' in the sense in which this expression is usually employed. As already mentioned, Mann (14) found no impairment of urea formation in animals in which the liver had been reduced to 20 per cent. of its normal size. In my experiments on human patients with diseases of the liver, a failure to form urea was found only in the advanced stages accompanied by jaundice and ascites. The post-absorptive increase of

urea in the blood of two of the diabetics studied was far smaller than in any of the other examples of liver disease, and the values in exophthalmic goitre, myxoedema, gout, hyperpiesia, and uraemia were also subnormal. It may well be that this is evidence of disturbance of protein metabolism in these diseases due to functional disorder of the liver. Nevertheless it is not the type of disturbance of liver function which the clinician expects to elicit from a test of hepatic efficiency, and one must conclude that these protein tests have no value in clinical medicine as a method of determining the degree of anatomical damage to the liver.

Conclusions.

1. The fasting amino-nitrogen of the blood is maintained at a level of 5·4 to 7·4 mg. per cent. with remarkable constancy in health and disease.

2. After the ingestion of protein or amino-acids the amino-nitrogen of the blood rises rapidly, reaching a peak in about two hours and falling to normal in six to eight hours. With the largest doses of amino-acid it has been found possible to give, the amino-nitrogen of the blood does not exceed 15–20 mg. per cent., the bulk of the amino-acid being taken up by the tissues.

3. The urea of the blood also rises after the ingestion of proteins or amino-acids. The maximum value is reached about two to four hours after the peak of the amino-nitrogen curve. In healthy subjects, after a dose of 50 grm. of protein or amino-acid, the blood-urea increases at least 50 per cent. above the fasting level.

4. In diseases of the liver, with the exception of acute yellow atrophy, the fasting and post-absorptive values of amino-nitrogen are normal. In acute yellow atrophy, liver-cells undergo necrosis and autolysis, and the absorption of this material may lead to an increase in the amino-nitrogen of the blood.

5. Urea formation is often normal in advanced disease of the liver.

6. In diabetes the blood-urea may fail to rise to the normal extent after the ingestion of large amounts of amino-acid. This is not the result of temporary disorder of the liver, as it has been found to persist over a period of months. It is not entirely remedied by the injection of insulin. Subnormal increase of the blood-urea has also been found in other conditions in which there is no disease of the liver in the accepted sense.

7. Tests based on the changes in amino-nitrogen or urea in the blood after the ingestion of proteins or amino-acids are of no value in the diagnosis of hepatic disease.

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STUDIES IN BLOOD AND URINARY CHEMISTRY DURING PREGNANCY[1]

BLOOD-SUGAR CURVES

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This preliminary paper is a review of the alterations that occur in the blood-sugar curves during pregnancy and the puerperium, not only as shown by a study of a collection of cases at the same stage of pregnancy, but also by following through individual cases from the early months to the puerperium. This latter method is important, as variations from case to case are great, and differences which are clearly demonstrated in the individual are not so marked when the average curves from groups of patients at the different time periods are studied.

The patients studied were all examined by an obstetrician. Clinically, pregnancy was described as normal when no symptoms were complained of, where the physical examination revealed no abnormality, the 24-hourly specimen contained no abnormal constituent, and where the patients were delivered of a healthy child, or had a still-birth which was attributable to mechanical causes.

In addition to these normal cases, many abnormal cases were examined. We will deal here with only the glycosurias. These cases were divided into: (1) Cases of symptomless glycosuria. (2) Cases of glycosuria with symptoms.

Cases of symptomless glycosuria, which are a very small percentage of normal cases (approximately 1 per cent. from the Out-Patient Clinic), we should prefer to classify as a subsection of normal cases.

All the glycosurias with symptoms have been excluded from this series and will be discussed in detail in a later communication. It is interesting to note the incidence of glycosuria cases: those in the present series (29 in all) were collected over a period of $2\frac{1}{4}$ years. The incidence is small, but an accurate percentage figure cannot be worked out as, for instance, only 2 out of the 8 cases with symptoms, came from the hospital out-patients, the other 6 being sent up from outside doctors and clinics: while of the cases without symptoms, 14 came from hospital and 7 from outside clinics. In previous work by one of us on 640 unselected pregnant women, an incidence of 5·4 per cent. of glycosuric cases was observed. We think this figure must represent a close approximation to the true incidence as the series was fairly large and many of the cases were subjected to repeated examination.

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Method of Examination.

The patients, after a preliminary clinical examination, reported at a later date for a sugar test in the morning, four hours after taking a cup of tea and a piece of bread and butter. It was found impracticable to make the patients report fasting from the night before, as many pregnant women cannot starve so long without feeling faint. The blood-sugar curves were obtained after a dose of 100 grm. of glucose in 200 c.c. of water, with the juice of a lemon. 100 grm. was given, as in our experience the maximum rise in blood-sugar levels is not always obtained after 50 grm. of glucose.

Sugar determinations were made over a period of 2½ hours, and specimens of urine were obtained at the end of the first and second hours and tested for the presence of sugar and acetone.

The blood-sugar was estimated by the Hagedorn and Jensen method and the presence of sugar in the urine detected by Benedict's qualitative reagent. The nature of the urinary sugar was determined by the preparation of the osazone. Quantitative estimations were made by Benedict's method.

Wherever possible a series of curves was obtained on the same woman. The curves were grouped in sections according to the length of duration of pregnancy, as follows: (1) Early months first to end of fifth month. (2) Later months, sixth month to full term. (3) After confinement.

This method has been adopted as it is generally thought that the sugar curves show certain differences in these periods.

For purposes of comparison the normal curve, range, and average for fifty healthy non-pregnant women, student volunteers, after 100 grm. of glucose has been found. The average resting sugar is 0·090 per cent.; the highest sugar value, 0·152 per cent., is reached half an hour after the ingestion of sugar, the curve then gradually dropping until at 2½ hours the value is 0·108 per cent. Two of these normals leaked sugar, one a trace, and the other 0·36 grm. per cent.

Classification of Cases.

(1) *Normal non-glycosuric cases.* Under the definition given above 43 cases have been studied. These have again been subdivided on the result of the sugar tolerance test into two groups:

(*a*) 17 cases with no sugar leak after 100 grm. of glucose.

(*b*) 26 cases with a sugar leak after 100 grm. of glucose.

In none of these cases was sugar found in a 24-hourly specimen on an ordinary diet. In fact the term 'sugar leak' is used to distinguish cases that pass sugar only after the ingestion of 100 grm. of glucose, from the true glycosurias, to be discussed later, that pass sugar on their ordinary diet as well as after the glucose meal.

2. *Symptomless glycosurias of pregnancy.* The 21 cases included in this group had sugar in varying amounts in the 24-hourly specimens upon a normal diet. These cases were further subdivided into the following groups:

(*a*) 4 cases of renal glycosuria. Blood-sugar values not raised above the average normal.

(*b*) 17 cases showing glycosuria due to raised blood-sugar values.

Non-Glycosuric Cases.

(43 Cases : 70 Curves.)

1. *Cases with no sugar leak.* (17 cases.) Referring to the lists below, the figures are given of the average values obtained from the whole group and the sub-groups as well as the range of sugar values. Both the average curves, and the range for the whole group in all three periods (1–5 months, 6–9 months, and post-confinement) approximate very closely to the average curve and range obtained from a series of healthy, non-pregnant women of the same ages as the pregnant cases.

The cases in Group 1 *a* yield an average curve during the first 5 months of pregnancy that is slightly higher than the normal non-pregnant curve, and, moreover, the rise to the maximum value is a little delayed. In the second section the curve is slightly lower, both relative to the normal and to the curves obtained in the first months of pregnancy and to the post-confinement period: however, it approximates very closely to the normal non-pregnant average. No individual curve, even post-confinement, rises above 0·197 per cent., and it is remarkable how very closely in the second part of pregnancy the maximum values approximate to the 0·150 per cent. line. Individual cases show a progressive lowering of the curve as pregnancy continues, a change that is very characteristic of all the non-glycosuric pregnant cases that we have yet followed through, if we exclude values obtained immediately pre-delivery (same day). After confinement the curves vary according to the time that has elapsed since delivery; in the early puerperium the curves are relatively much higher than after the lapse of 3–4 weeks. It may be that these high curves are associated with absorption of blood clot or minor sepsis.

To sum up, our findings in this group suggest that during the first period of pregnancy the blood-sugar curves are very slightly raised, and that they then become progressively lowered as pregnancy continues, to be restored to normal values again after delivery.

2. *Cases with sugar leak.* (26 cases.) The cases in this group show a much greater range of sugar values, and probably in a larger series would be divided yet again into two sub-groups, those with a low maximum blood-sugar value (e. g. under 0·150 per cent.) who must leak by virtue of a lowered renal threshold, and those with high maximum blood-sugar values (e. g. above 0·150 per cent.) which show a definite tendency to raised blood-sugar curves, and leak possibly through a combination of lowered threshold and diminished tolerance. It must be emphasized that although these curves have a slightly wider range than those in Group 1 *a*, they still fall well within the range found in normal non-pregnant women. In this group the lowering of the curve that occurs in

individual cases as pregnancy progresses is masked in the average curves by the wide range of values obtained from different patients and the fact that not sufficient cases have been followed through. Unfortunately there are too few post-confinement curves from which to generalize.

The amount of sugar passed after 100 grm. of glucose was in the majority of cases negligible and varied from traces to 0·4 per cent. glucose. After confinement no case leaked sugar after the 100 grm. of glucose, though some of the curves were on a higher level than during pregnancy, a fact that can only be explained by an alteration in renal threshold.

In these two normal groups a trace of acetone was found once in one patient's 24-hourly specimen, otherwise it was never present in any patient.

To sum up: in all the non-glycosuric cases (Groups 1 *a* and 1 *b*) at all stages the blood-sugar values fall well within the range obtained from normal non-pregnant women; the renal threshold, however, must be definitely lowered in a large majority of the cases as 60 per cent. leak sugar after the glucose meal, whereas only 5·4 per cent. of normal non-pregnant women leak, and yet the average curves in the two classes of cases are practically identical. None of the 60 per cent. of cases continued to leak sugar after confinement, although the sugar curves were on a higher level than the sugar curves found during pregnancy. This shows that after confinement the renal threshold returns to the normal level.

Cases of Symptomless Glycosuria.

(21 Cases : 64 Curves.)

1. *Renal glycosuria.* (4 cases.) In this group all the 21 cases passed glucose in their ordinary specimens (3 passed acetone when first seen, but none later) and were otherwise regarded by the obstetrician and us as normal.

Renal glycosuria. Four cases are included in this group. The sugar curves show that after 100 grm. of sugar, the highest average figure in the first period is 0·163 per cent., in the second only 0·144 per cent.; yet on these low levels the percentage of sugar in the urine varied from 1–11·6 per cent. of glucose.

These post-confinement cases did not leak, though the curves now show an average maximum figure of 0·161 per cent. During pregnancy these cases had persistently passed glucose in their 24-hourly specimens, the maximum concentration on ordinary diet being 1·5 per cent. Hence in these cases not only is the sugar curve lowered but also the renal threshold, through some agency functioning at this period and not through some congenital abnormality as in non-pregnant renal glycosurias. Note should be taken of the fact that the excessive lowering of the threshold persisted throughout pregnancy, and was sufficient to cause a continual glycosuria though the level of the curves fell as pregnancy progressed. Probably these cases show merely an extreme degree of the normal lowering of the renal threshold that occurs in pregnancy.

2. *Cases with raised sugar curves.* (17 cases.) In this group the average rise in all three periods is much greater than in the previous groups, a difference which is particularly marked in the post-confinement curves. The average curves show that in the first period the peak reaches 0·168 per cent., in the 6–9 months period, 0·195 per cent., and the post-confinement maximum reaches the even higher value of 0·216 per cent.

Though the average values are not greatly increased during pregnancy, the range is markedly greater, and further there is not the progressive lowering of the curves which is characteristic of the completely normal. Whether, if a longer series were followed through, some cases would show a fall, we cannot say, but in the actual cases studied, the values either remained the same or showed a slight rise.

The high curve is not, however, associated with a raised fasting level or a markedly delayed fall, except in a few cases. In fact the curves resemble somewhat exaggerated 'McLean lag' curves, though the fall is slower than usual in this type, as in no case is the value down in 1½ hours, and the average value 2½ hours after the glucose is about 0·125 per cent. in all periods.

On examining the 12 cases that reported after confinement it was found that after 100 grm. of glucose, 6 did not leak, and 6 leaked glucose. The former cases show relatively lower curves after confinement (24-hourly specimens, no sugar leak) though the individual lowering in certain cases is very slight. But, what is very striking, is the difference between these cases and those which continue to leak sugar after confinement, upon a 100 grm. dose. In these cases the average post-confinement curve is very much raised (see list), and in individual cases the increase in the maximum values may be as great as 0·184 mg. For example, one particular case gave post-confinement a resting blood-sugar value of 0·080 per cent., but this rose in half an hour to 0·279 per cent., and in 1½ hours to 0·385 per cent., but at 2½ hours was 0·115 per cent. During pregnancy she gave a similar type of curve, but the rise (maximum value 0·216 per cent.) was not so high. She leaked sugar after both tests, but much less on the higher curve, after confinement, demonstrating yet again the typical lowering of threshold that occurs during pregnancy.

In spite of the raised curves persisting in these cases we do not consider the condition requires any treatment other than the correct spacing of the carbohydrate in the diet; the level of the blood-sugar is by this means kept within reasonable limits, and very much lower than the values found after the 100 grm of glucose.

In all cases both mother and child were healthy and progressed satisfactorily (many of the cases have been followed up for a period of two or more years), and many of the women had had previous normal pregnancies with the exception of their glycosuria. Future progress of the cases will be carefully watched.

Discussion.

Many theories have been advanced to explain the changes that take place in carbohydrate tolerance during pregnancy, but few authorities have based their conclusions on a study of a series of normal cases and the explanations of the glycosurias of pregnancy are highly speculative.

Herold (1), writing on normal pregnant women, has advanced the theory that during the earlier months there is an over-activity of the sympathetic nervous system and its associated ductless glands, including the corpus luteum, whereas in the later months there is an increase in the activity of the vagus and its associated glands. These changes are said to lead to the fasting blood-sugar values being practically normal in the earlier months, but progressively lowered as pregnancy continues, except that immediately before and during delivery there is a relative hyperglycaemia. During the puerperium there is, according to this author, still an increase in vagotonus which causes low resting blood-sugar values. In the earlier months renal glycosuria is more frequent and is called into being through a lowered threshold for glucose. Küstner's (2) animal experiments support this view. Later, Herold thinks the renal threshold rises again. No sugar curves are given in the paper.

Elias, Gudeman, and Roubitschek (3) have shown in a series of very neat observations on pregnant women that in the earlier months, though the rise in the blood-sugar curves after the intravenous injection of glucose is practically the same as in normal non-pregnant women, the leak point is definitely lowered. This was determined by a series of simultaneous sugar estimations in blood and urine, the latter obtained by continuous catheterization. The authors have also shown that insulin does not lower the blood-sugar to the same extent in the early months of pregnancy as in the non-pregnant condition. They advance no theory to account for their observations.

We have been unable to confirm Herold's observations on the alteration in the fasting blood-sugar level as pregnancy proceeds, as in our series the individual variation is too great. But many of our normal non-glycosuric cases, and the pure renal glycosurias, do show a progressive lowering of the blood-sugar curves as pregnancy progresses and individual cases that were studied immediately before delivery show a rise then in their sugar curves. Post confinement, however, the curves tend to be higher in the earlier puerperium than after the lapse of several weeks or months. Cases 13 and 16. The rise in renal threshold that Herold thinks takes place as pregnancy progresses was not observed in our cases, the fact was rather the opposite, as in spite of lower curves in the latter months, no case that leaked in the earlier months ceased to leak as pregnancy progressed. Like Elias and his co-workers we find that the blood-sugar curves after the ingestion of glucose (they injected the glucose in their cases) are in normal non-glycosuric cases in the early months practically the same as in the normal non-pregnant woman, and we agree with these authors that there is

normally a lowering of the renal threshold in this period. Further, we find that throughout normal pregnancy and the puerperium the blood-sugar curves in non-glycosuric cases are well within the normal range.

Höst (4) from his observations on pregnant women considers that during the early months the glycosuria that occurs after 50 grm. of glucose is due to a raised curve, and not to a lowering of the renal threshold, whereas in the latter half of pregnancy there is an increase in carbohydrate tolerance associated with a lowering of the blood-sugar curves, but at the same time a lowering of the renal threshold which gives rise in many cases to glycosuria after the sugar-meal. His figures differ markedly from ours, as in all cases the values he quotes are higher (he states that in early months some of his cases have diabetic curves) but they show the same progressive lowering as pregnancy progresses. We think it possible that he did not exercise sufficient care in selecting normal cases as we have found similar high values in certain of the minor toxaemias of pregnancy (e. g. vomiting).

The alteration in renal threshold that Herold and many others postulate, and which was so beautifully demonstrated by Elias and co-workers, could not be shown in all cases by our method of examination as in about 40 per cent. of the normal non-glycosuric cases, even after 100 grm. of glucose, the blood-sugar values do not reach the leak point. Further, the lowering cannot be very marked, as glycosuria, contrary to the teaching of many authorities (Lambie (5) &c.), is an infrequent complication of pregnancy. But it is clear from a study of the non-glycosuric cases that leaked after 100 grm. of glucose, that there is an alteration in the threshold, as post confinement these cases ceased to leak sugar after the same dose of glucose, though the blood-sugar curves were practically identical.

When the question of incidence and cause of glycosuria in pregnancy is considered, very divergent views have been expressed and it is unfortunate that our results only add to the number of conflicting figures.

Höst has given the incidence of glycosuria in a series of non-pregnant women and finds a remarkably high percentage of cases that leak after 50 grm. of glucose, e. g. 26 per cent. of his normal non-pregnant as compared with 5 per cent. in our series, and as high a figure as 61 per cent. in the early months and 37 per cent. in late months of pregnancy, figures which are the converse of our findings. We would criticize his normal series as they consisted of hospital patients who were presumably attending for some pathological state. It is difficult to compare his pregnant cases with ours as his time divisions are different, and we had few cases which were normal reporting before the third month.

Lawrence (6) from a series of 24 cases of glycosuria occurring in pregnancy, after the exclusion of 5 cases of a diabetic nature, gives the following findings: 19 cases with normal sugar curves of which 16 showed a lowered renal threshold, 2 gave lag storage curves (height not quoted but included among normal curves) and one a case of lactosuria. These findings are remarkably different from our own. In a series of 29 cases of glycosuria, 8 are excluded, as being either

definitely diabetic or suffering from some other abnormal condition. The remaining 21 cases consisted of 4 cases of renal glycosuria, and 17 cases with abnormally raised curves, some approximating to the lag type but none typical. In no case that was detected clinically before delivery as passing sugar was that sugar lactose.

These findings and a study of the curves obtained in the normal cases that leaked after 100 grm. of glucose, but not on an ordinary diet, would suggest that far the commonest cause of glycosuria in pregnancy is an alteration in carbohydrate tolerance, that causes a very definite increase in the blood-sugar levels after 100 grm. of glucose, though in nearly all the cases the resting sugar is normal and the value returns to normal in 2½ hours. This increase, associated as it is with the lowering of renal threshold that seems to occur in all cases, causes in certain instances marked glycosuria. Whatever is the cause of this alteration in carbohydrate tolerance, and we are not prepared to discuss it here, it is one that persists after pregnancy, as the cases all show the same raised curve or a higher rise (more abnormal curve) after delivery even many months later. That the condition is not serious is seen by the fact that all the patients included in this series had normal children and gave histories of repeated normal pregnancies.

Finally, though our work does not show it conclusively, the fact that the post-confinement curves in all classes show an average higher value than those obtained during pregnancy (with the exception of the average curve for certain non-glycosuric cases, Group 1 *a*, during the first five months) would suggest that both in the completely normal and in the cases of symptomless glycosuria, the blood-sugar values are relatively lower than those obtained from the same case in the non-pregnant state. The rise in the curve post confinement even months later is very strikingly seen in some of the glycosuric cases. The figures summarize the alterations that occur in the blood-sugar curves of the different groups of cases both relative to the normal non-pregnant curve and also to each other.

Conclusions.

1. The blood-sugar curves of normal non-glycosuric pregnant women in all periods of pregnancy and the puerperium fall well within the range of curves obtained from normal non-pregnant women.

2. The blood-sugar curves in normal non-glycosuric pregnant women tend to drop as pregnancy progresses, then to rise in the early puerperium and return to normal in a few weeks time.

3. The renal threshold would appear to be lowered in the majority of normal pregnant women, probably in all, but this could not be shown conclusively by our methods.

4. The incidence of symptomless glycosuria on an ordinary diet is 5·4 per cent. of all pregnant women (640 cases).

5. The incidence of renal leaks after 100 grm. of glucose in normal non-glycosuric, pregnant women is 60 per cent.

6. As far as the normal cases have been followed through, no case that leaks sugar in the early months, either on ordinary diet (true glycosuria) or after a sugar test, ceases to leak as pregnancy progresses.

7. The lowering of the renal threshold, though a factor in all the glycosuric cases, is not the major one in its causation of the glycosurias of pregnancy, but rather it is the association of the lowered threshold with an abnormally raised blood-sugar curve. Only 4 out of 21 cases of glycosurias were simple renal leaks.

8. The curves of the normal glycosuric cases are not diabetic in type but approximate rather to exaggerated ' lag ' curves.

9. In these glycosuric cases, excluding the true renal leaks, the curves rise as pregnancy proceeds.

10. The raised curves found in the majority of the glycosuric cases persist after pregnancy, though the glycosuria may disappear owing to a rise in the renal threshold for glucose.

11. The simple glycosurias of pregnancy described above would appear to be of slight significance, as the cases have normal pregnancies and normal children on diet in which carbohydrate is spaced.

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TABLE I.

Normal Pregnant Women. No Sugar Leak after 100 grammes Glucose. Group 1 *a*.

No.	Age	Multip.	1–5 Months.	6–9 Months.	Post.
1	28	1	081, 107, 125, 170, 152, 143, 125, 098	—	—
2	32	2	081, 116, 147, 143, 125, 089, 067, 063	—	—
3	31	2	081, 134, 170, 188, 161, 125, 125	—	—
4	29	4	090, 107, 143, 161, 143, 125, 107, 098	—	129, 197, 183, 138, 143, 136, —, 136
					089, 152, 185, 161, 165, 120, 130, 130
5	33	1	086, 107, 143, 175, 179, 179, 134, 125	071, 125, 143, 125, 098, 116, 125, 134	090, 116, 116, 107, 116, 161, 161, 143
			091, 116, 161, 161, 152, 125, 134, 107	081, 125, 161, 170, 170, 147, 129, 147	097, 144, 142, 137, 115, 130, 107, 114
6		3	080, 129, 129, 120, 111, 107, 085	090, 098, 134, 161, 170, 140, 111, 124	095, 123, 157, 112, 117, 094, 099
			090, 125, 134, 152, 143, 107, 107		
7	24	0	099, 116, 122, 170, 161, 143, 125, 099	—	—
8		0	—	081, 098, 134, 125, 116, 081, 107, 098	—
9	25	0	—	095, 112, 143, 166, 161, 134, 120, 116	089, 134, 165, 174, 139, 12 124
10	31	6	—	081, 134, 143, 152, 152, 134, 116, 116	077, 121 ,159, 159, 134, 11 088, 096
11	22	0	—	098, 161, 161, 143, 143, 143, 107, 107	—
12	32	1	—	098, 115, 161, 161, 161, 107, 103, 104	—
13	21	0	—	089, 142, 169, 142, 136, 133, 124, 089	089, 143, 170, 188, 179, 166, 148, 143 *
				081, 116, 143, 125, 134, 125, 116, 107	098, 143, 143, 138, 129, 092, 093, 120
				070, 118, 121, 116, 121, 112, 109, 116	
14	24	0	—	107, 071, 094, 125, 139, 116, 098, 134	—
15	23	0	—	—	107, 152, 152, 152, 143, 143, 143, 125
16	27	0	—	076, 127, 148, 154, 179, 152, 147, 130	083, 134, 194, 238, 222, 213, 204, 208 *
					103, 113, 130, 148, 113, 139, 117, 121
17	23	0	—	—	107, 152, 152, 152, 143, 143, 125
	Average		086, 120, 145, 161, 149, 130, 111, 101	086, 118, 143, 143, 144, 126, 116,117	098, 140, 153, 143, 132, 127, 117, 123

Normal Pregnant Women, with Sugar Leak after 100 grammes Glucose. Group 1 *b*.

1	45	7	090, 134, 161, 161, 161, 161, 098, 081	—	093, 163, 174, 134, 125, 093, 104, 111
2	31	—	—	099, 125, 161, 170, 161, 103, 134, 081	—
3	28	0	090, 134, 143, 143, 125, 125, 143, 125	093, 108, 119, 128, 137, 126, 133, 128	—
4	24	0	086, 145, 150, 150, 116, 152, 107	—	—
5	29	1	—	091, 107, 116, 125, 116, 116, 107, 115	—
				072, 107, 134, 162, 107, 134, 116, 098	
6	21	0	—	079, 102, 123, 114, 116, 092, 102	—
7	22	1	—	116, 143, 161, 170, 161, 161, 152, 134	—
8	29	1	—	090, 107, 116, 134, 116, 125, 116, 107	—
9	22	0	—	081, 103, 130, 132, 161, 152, 152, 134	—
10	29	2	—	081, 116, 152, 188, 179, 143, 134, 125	094, 155, 199, 161, 152, 152, 134
				069, 129, 170, 180, 166, 139, 112, 112	
11	25	0	—	089, 098, 134, 179, 161, 152, 160, 143	—
12	31	8	—	081, 116, 159, 183, 161, 134, 161, 125	—
13	28	1	—	099, 139, 188, 202, 179, 134, 134, 134	—
14	27	1	—	098, 134, 170, 161, 125, 161, 205, 152	094, 094, 131, 151, 161, 151, 124, 095
15	26	0	—	111, 138, 165, 169, 174, 143, 155, 138	—
16	23	0	—	072, 098, 161, 207, 198, 143, 125, 107	—
17	29	2	—	086, 149, 152, 162, 156, 138, 142, 133	072, 111, 156, 182, 216, 183, 165, 143 *
18	28	1	084, 143, 170, 179, 161, 161, 107, 125	107, 156, 183, 179, 188, 165, 170, 149	081, 143, 197, 197, 179, 109, 109, 090
			081, 116, 179, 188, 170, 116, 152, 121	072, 120, 183, 193, 193, 174, 156, 093	
19	22	0	—	098, 134, 179, 170, 208, 143, 134, 125	093, 147, 165, 174, 188, 156, 138, 116
20	33	1	—	106, 143, 168, 193, 161, 170, 143, 134	107, 152, 197, 154, 129, 155, 116, 116
21	33	1	—	096, 157, 150, 139, 189, 157, 152, 126	
				098, 143, 161, 152, 152, 152, 143, 134	
				115, 160, 178, 178, 169, 124, 115	
22	31	1	—	091, 160, 203, 125, 148, 146, 130, 114	098, 142, 187, 204, 216, 196, 187, 169 *
				089, 116, 152, 161, 178, 152, 124, 116	
23	33	2	—	091, 139, 152, 179, 180, 170, 108, 119	
	Average		084, 134, 160, 164, 146, 143, 121, 113	101, 127, 161, 163, 160, 143, 139, 123	094, 143, 177, 162, 157, 135, 121, 105

* Cases within 10 days of delivery not included in average.

Table II.

Cases of Symptomless Glycosuria.

No.	Age.	Parity.	1–5 months.	6–9 months.	After	
Cases with Raised Curves.						
1	—	0	089, 115, 160, 160, 142, 160, 142, 124	—		—
2	40	6	—	107, 137, 154, 196, 227, 196, 187, 127		—
3	31	8	—	081, 116, 159, 183, 161, 134, 161, 125		—
4	21	0	—	093, 116, 179, 202, 198, 111, 099, 080		—
5	27	1	—	113, 136, 170, 143, 161, 113, 073, 074		—
			Average	098, 126, 165, 181, 187, 138, 130, 101		
Post Confinement. Sugar Leak.						
6	42	7	—	098, 103, 198, 251, 236, 253, 236, 174	3 months	093, 186, 271, 269, 281, 248, 162, 141
					3–9 months	098, 187, 263, 304, 293, 224, 178, 115
					after 2nd conf.	098, 132, 257, 267, 247, 227, 098, 054
7	28	0	—	111, 196, 238, 209, 166, 130, 107, 102	10 days	098, 187, 196, 196, 169, 098, 089, 107
				077, 107, 148, 157, 196, 206, 170, 090	3–9 months	092, 132, —, 173, 190, 144, 093, 092
					,, ,,	128, 191, 238, 278, 258, 155, 119
					,, ,,	110, 190, 199, 177, 114, 114
8	42	3	068, 175, 203, 207, 198, 166, 107, 090	086, 194, 188, 216, 207, 188, 152, 116	3 months	080, 187, 279, 304, 385, 205, 115
					9 mths.–2 yrs.	089, 169, 224, 243, 215, 143, 124, 107
9	42	1	—	114, 178, 215, 208, 225, 170, 134, 115	9 mths.–2 yrs.	129, 202, 230, 260, 230, 174, 164, 120
				085, 112, 162, 185, 194, 175, 122, 076		
10	33	2	100, 119, 179, 200, 210, 137, 137, 128	099, 161, 179, 188, 207, 212, 197, 152	10 days	116, 152, 175, 189, 222, 198, 179, 179
				102, 129, 156, 174, 156, 138, 093	3 months	104, 118, 134, 251, 258, 263, 241, 170
					3–9 months	115, 142, 201, 243, 278, 165, 148, 115
						101, 119, 179, 200, 210, 137, 137, 128
11	29	—	—	098, 160, 087, 215, 215, 205, 196, 160	10 days	090, 170, 226, 226, 255, 255, 245, 179
				080, 116, 161, 189, 213, 208, 170, 134	3–9 months	129, 148, 218, 254, 266, 198, 198, 143
				098, 134, 152, 170, 141, 179, 198, 179		
				072, 134, 170, 198, 246, 226, 188, 090		
			Average	093, 144, 179, 197, 200, 191, 163, 126		098, 163, 219, 239, 230, 184, 152, 127

Post Confinement.			*No Sugar Leak.*			
12	31	0	089, 134, 121, 134, 134, 198, 198	059, 130, 175, 179, 188, 188, 196, 116	10 days	107, 178, 179, 193, 198, 179, 143, 098
				081, 152, 181, 189, 208, 175, 134, 108	3 months	107, 170, 177, 177, 207, 177, 099, 072
					3–9 months	081, 152, 188, 207, 203, 152, 107
					9 mths.–2 yrs.	107, 180, 192, 207, 197, 170, 125
					,, ,,	107, 161, 161, 179, 190, 170, 152, 134
					2 years	100, 182, 211, 211, 173, 145, 154, 163 †
13	34	3	—	090, 152, 161, 179, 188, 217, 179, 161	3 months	096, 123, 174, 179, 166, 150, 123, 118
					3-9 months	116, 152, 179, 152, 143, 116, 152, 107
14	39	1	—	107, 170, 217, 237, 237, 237, 247, 198	10 days	129, 193, 212, 222, 213, 208, 177, 105
				083, 122, 174, 188, 197, 214, 184, 150	3–9 months	115, 151, 160, 179, 160, 115, 115, 115
15	30	0	—	090, 125, 179, 206, 212, 170, 188, 196	10 days	129, 174, 212, 174, 174, 193, 174, 129
					3 months	090, 179, 198, 161, 170, 143, 152, 134
					3–9 months	080, 152, 170, 152, 134, 152, 825, 081
16	43	4	—	089, 152, 198, 179, 161, 116, 107, 107	3 months	089, 205, 205, 215, 205, 178, 161, 142
					,,	110, 155, 196, 210, 146, 160, 142, 128
					3–9 months	089, 142, 160, 178, 187, 133, 142, 116
					9 mths.–2 yrs.	090, 079, 207, 226, 179, 171, 152, 152 ††
17	26	1	—	089, 120, 147, 156, 161, 159, 134, 127	10 days	105, 127, 172, 207, 202, 201, 163, 109
				077, 166, 182, 175, 182, 165, 114	3 months	098, 143, 152, 143, 152, 116, 143, 098
			Average	095, 143, 179, 198, 198, 182, 165, 144		103, 166, 187, 184, 179, 159, 141, 112
			Cases 1–17. Average	095, 141, 177, 195, 195, 179, 150, 128		100, 164, 199, 211, 204, 171, 146, 119
Renal Leaks.						
18	26	1	089, 134, 179, 179, 143, 125, 134, 134	076, 129, 143, 147, 144, 125, 115, 124	3 months	103, 121, 121, 116, 116, 114, 096, 118, 105
				099, 152, 161, 161, 134, 125, 107, 116		
19	31	1	080, 120, 160, 160, 160, 114, 098	098, 116, 134, 143, 134, 124, 081, 081	10 days	103, 135, 200, 130, 148, 139, 103
			080, 134, 152, 143, 143, 143, 134, 099	071, 098, 116, 134, 134, 107, 116, 071	3 months	098, 107, 143, 170, 170, 170, 143, 134
					,,	091, 130, 177, 168, 180, 139, 125, 112
20	29	0	—	090, 125, 143, 143, 134, 134, 134, 099	,,	099, 161, 171, 179, 198, 143, 143, 134
21	28	1	089, 125, 162, 170, 170, 116, 152, 134	100, 141, 154, 132, 132, 123, 116, 096	,,	081, 099, 125, 170, 143, 125, 125, 081
		Average	084, 128, 163, 163, 154, 124, 129, 122	088, 128, 144, 144, 138, 123, 114, 106		094, 125, 155, 155, 169, 134, 126, 113

† Raised curve ? due to worry about possible pregnancy.
†† ,, ,, ? due to extraction of teeth for pyorrhoea. (Omitted from Average.)

Average for 50 Normal Non-Pregnant women after 100 grammes Glucose. 091, 137, 152, 146, 139, 122, 115, 108.

THE SPECIFIC OXYGEN CAPACITY OF THE BLOOD-COLOURING MATTER IN PATHOLOGICAL CONDITIONS[1]

By H. ENGELKES

(From the Medical Clinic of the University of Utrecht)

Introduction.

During recent decades many investigators have been occupied with the question as to whether or not the amount of oxygen which the unit of blood-colouring matter can hold, when saturated with it to the maximal amount, is always the same under all circumstances. We shall not here enter into the long discussion which has taken place on this question.

At the present time the opinion is almost universally held that the maximal amount of oxygen which haemoglobin under normal circumstances is able to absorb is to the extent of 1 atom of iron to 2 atoms of oxygen: in other words *the specific oxygen capacity* (the number of c.c. oxygen, dry, at 0° and 760 mm., absorbed per gramme of iron) is 401 (1).

The belief that this relationship remains unaltered under pathological circumstances, and especially in certain blood diseases, is increasingly gaining ground. It is based chiefly on the investigations of Butterfield (2) who came to the conclusion after making very accurate investigations in a number of persons, that the light-absorption, iron content, and gas-absorbing power of human haemoglobin are constant quantities (within the limit of faults of method), not only in physiological conditions, but also in blood diseases like polycythaemia, pernicious anaemia, chlorosis, scurvy, and the so-called pseudo-leukaemia. I shall refer to these investigations and those of others later on in discussing the results.

The question has been put whether this conclusion can be accepted in such a general way. It has been pointed out from various quarters that under pathological conditions, altered metabolic products of haemoglobin may be present, which have retained the iron but lost the power to bind oxygen; and both Dutch and English investigators have found methaemoglobinaemia and sulphaemoglobinaemia in various conditions where there was no question of exogenetic poisoning. Schumm observed haematinaemia in cases of pernicious anaemia. Hijmans van den Bergh (3, 4) and Snapper (5), and subsequently many others, have confirmed Schumm's observation. It is difficult to believe that the blood in these cases has kept its normal specific oxygen capacity.

[1] Received December 19, 1928.

Since the investigations which I am going to refer to are not easily accessible (they have been published in Dutch), I shall describe them as shortly as possible.

Method of Procedure.

Blood from the congested vein of the arm is collected in a sterile bulb in which it is defibrinated by means of glass pearls; after that it is centrifugalized in isotonic salt solution and washed twice. The emulsion is laked by the addition of twice its volume of diluted ammonia (4 c.c. liq. amm. fortis caust. to 1 litre of aq. destillata) and centrifugalized. The clear solution thus obtained is then examined as to its oxygen-binding power, and the amount of iron it contains. The examination as to the amount of oxygen was carried out in Barcroft's differential apparatus for 1 c.c. of blood.

To make it saturated the solution was rotated with oxygen in a tonometer for 45 minutes at room temperature by means of a motor.

Usually eight parallel analyses were carried out in four sets of apparatus; in some cases the number was six.

The apparatus was accurately standardized in various ways (physical method of Barcroft and Higgins, Barcroft and Burn's chemical calibration method, and Münzer and Neumann's method).

The iron determination was always carried out in duplicate. In each of two Kjeldahl bulbs 10 to 20 c.c. of the above-mentioned solution was evaporated to dryness, after which it was turned to ash with Neumann's acid mixture (equal parts of concentrated H_2SO_4 and HNO_3) of which the iron content was accurately estimated. After driving off the last traces of HNO_3, boiled water was added up to 150 c.c., after which (while CO_2 was being introduced into the solution) it was cooled in iced water, and titrated with titanious chloride, potassium sulphocyanide being used as indicator, and CO_2 being continually introduced. In the calculation corrections were made for the iron contained in the acids used of which the exact amount was known.

Clinical Observations.

A. *Normal persons.* In five normal persons results were obtained which are recorded in Table I. They are altogether in agreement with the conception of a constant specific oxygen capacity of unaltered haemoglobin.

One must not conclude from this, that the blood of all healthy people under all circumstances will show the same relative proportions: it is quite possible that in some individuals, otherwise altogether healthy, methaemoglobin or other altered blood products may be found in the circulation, which substances would cause a drop in the specific oxygen capacity. That this is in fact the case in animals, will be shown in the following pages.

B. *Intraglobular sulphaemoglobinaemia.* I was in a position to examine the blood of several patients, suffering from intraglobular sulphaemoglobinaemia while making these investigations (Table II).

Case I. K. V. 17 years old, flower-seller, had, according to his mother, practically never defaecated spontaneously. Hence the intestine was being washed out once a week. He complained much of headache, nausea, and vomiting. Latterly the mother had noticed cyanosis.

The patient was remarkably small for his age and looked intensely cyanotic, the cyanosis changing greatly at different times. Besides showing various signs of infantilism the patient had very evident clubbed fingers and toes. The temperature, pulse, and respiration were normal. There was no abnormality in the thoracic organs. The abdomen was much enlarged and a Röntgen examination showed that the left side of the abdomen was largely filled up by a tremendously enlarged sigmoid flexure of the colon. The diagnosis was *Hirschsprung's disease.* The urine contained a trace of indican, but an ordinary examination did not reveal any other abnormal ingredients. There was no noticeable dyspnoea, but now and then it was noticeable on effort (perhaps caused by the high position of the diaphragm?). A spectroscopic examination of the skin on which the light fell—still better the lobe of the ear, the cheek, or a fold of the scrotum, through which light passed, showed a spectrum with a band running through the red. Examination of the blood showed the presence of an intraglobular sulphaemoglobinaemia. The serum contained neither sulphaemoglobin, methaemoglobin nor haematin, and a normal amount of bilirubin.

In this boy the specific oxygen capacity (S.O.C.) was twice determined: the first time it was 324, the second time (after the intestine had been repeatedly washed out) 361. The S.O.C. showed thus a deficit of 19 per cent. and 10 per cent. respectively.

Case II. Mrs. S. D. Diagnosis: *Retro-uterine haematocele.* This woman was 40 years of age and married. She acquired gonorrhoea when she was 16 years old, and was infected with syphilis in her second marriage. She had menstruated irregularly since August 1919. On January 1, 1920 she was seized with a severe attack of abdominal pain, accompanied with an inclination to vomit and with tenesmus. Defaecation became difficult and painful. The patient was very ill, not cyanotic or icteric. The abdomen was much stretched and swollen, especially in the epigastrium and hypogastrium; percussion sound was tympanitic; there was no visible peristalsis. A vaginal examination revealed a slight resistance in the pouch of Douglas. The patient was treated with enemata, and flatus and stools were passed. After this treatment the condition was at first much better and the abdomen softer. The intestine, however, still remained imperfectly emptied. At last the attempt to obtain more or less satisfactory defaecation was successful. On January 9 symptoms resembling those of ileus were present: visible intestinal peristalsis, loudly audible intestinal movements, and a swollen abdomen. The urine contained a trace of albumin and no indican.

Examination of the blood: serum showed a strongly positive Wassermann reaction, no haematin, a normal amount of bilirubin. The haemolysed red blood corpuscles showed an intense sulphaemoglobin spectrum, that could also be observed on the lobe of the ear when traversed by rays of light. The patient did not show any sign of cyanosis. At the operation a retro-uterine haematocele was found with an enlarged and ruptured tube. It was found that the specific oxygen capacity was 356, hence there was a deficit of 11 per cent. Some months after the operation, after the patient had recovered, the sulphaemoglobin spectrum was found to have disappeared. For various reasons it was not possible to repeat the examination of the blood.

Case III. Mrs. S., 52 years old. Diagnosis: *carcinoma mammae, with metastases pressing on the brachial plexus and the lumbosacral plexus; intraglobular sulphaemoglobinaemia.* This patient was observed in the clinical wards of Professor Snapper, who generously gave me the opportunity of making

an examination of the blood. The specific oxygen capacity was in this case 312, hence when saturated to its maximal degree, its capacity was 22 per cent. below normal. The history of this patient is included in Professor Snapper's article and van Vollenhoven's treatise.

Here I must shortly refer to the occurrence of a spontaneous intraglobular sulphaemoglobinaemia in animals, mention of which has been made on a previous page.

This observation is of importance in forming a right conception about the S.O.C. of the blood under normal conditions. In an investigation into the pathogenesis of the sulphaemoglobinaemia we saw that in a number of rabbits seemingly quite healthy, a sulphaemoglobinaemia spectrum had been observed. We examined 55 rabbits of varying origin.

In Table III it is seen that in the cases 3, 13, 14, and 33 an intense band in the red was observed, even clearly visible in the circulating blood in the transilluminated ears; in other cases this was less clearly evident; in the great majority it was negative.

If we look upon the weakly positive and the doubtful reactions as negative, then there still were 11 clear cases of sulphaemoglobinaemia (of which 4 were strongly positive) in 55 rabbits. The animals were of very varied origin. This made it unlikely that varying external circumstances were the chief factor in the causation, although it deserves attention that among 25 animals out of the same institute (that of Professor Wester) the sulphaemoglobinaemic spectrum was only observed in one case. With the knowledge which we have about it, it is not possible to find out whether race, sex, age, or diet have played a part in the matter. For that a more systematic examination is necessary. I will only point out that of the ten animals which we observed for months, those which had the abnormality retained it, whereas in the others with a normal spectrum the sulphaemoglobinaemia spectrum was never found. Both groups lived in the same hutch, under exactly the same conditions of life, such as feeding, &c. Hence we are easily led to make the supposition that the cause of the condition is not to be found in the external conditions of life, but more probably, in the individual differences between the animals themselves. We can exclude the supposition that the sulphaemoglobinaemic spectrum might have arisen outside the organism after extraction of the blood, because of the fact that in four animals the band was observed in the circulating blood, by lighting up the doubly folded ears with a carbon point lamp.

The blood spectroscopy was carried out by means of a Schmidt-Haensch hand spectroscope, using 1 part of blood to 3 parts of water (thickness of layer 1 cm.) and afterwards in still more dilute solutions. In the third rabbit the S.O.C. was determined in blood taken from the aorta and from the portal vein (which had been congested by a ligature made as near as possible to the portal fissure), being drawn into sterile syringes.

Not more than 7 c.c. of blood could be taken from the vena portae, so that only four gas analyses were possible. The S.O.C. was 362 in the aorta, 350 in

the vena portae, hence it was in both vascular systems evidently diminished, probably equally so in both.

Anaemias.

Schumm has pointed out the frequent occurrence of haematinaemia in various forms of blood destruction. It has been proved that there is a great difference as far as the haematinaemia is concerned, between the so-called secondary anaemias (e. g. the posthaemorrhagic) on one hand, and the haemolytic anaemias (e. g. pernicious anaemia, malaria, &c.) on the other hand: whereas one never finds haematinaemia in the first mentioned, one finds it very often in the latter class of cases.

It was important in our case to compare the S.O.C. of those two forms. In Table IV the reader will find the results of an examination of seven cases of secondary anaemia (low bilirubin content of the serum, no haematinaemia, no urobilinuria, low colour index). In these cases the final results showed no more aberration from the normal figures than could be accounted for by faults of method, so that one can safely say that the S.O.C. was maintained. On the other hand, the proportions were less simple in some haemolytic anaemias. For this examination some undoubted cases of pernicious anaemia (Table V) and two of malaria (Table VI) were chosen.

Patients 1, 2, and 3 who were in the stage of blood destruction (hyperbilirubinaemia and haematinaemia respectively) showed an evident fall of the S.O.C. Cases IV, V, and VI who had been taken into the clinical wards during a period of blood destruction, were in a stage of remission when the gas analysis examination was made: in them a normal S.O.C. was found.

In the three following patients (7, 8, and 9) the S.O.C. was determined both during the attack and also during the remission.

In W. van T. (Case VII) a fall of the S.O.C. was found during the attack, but not in the remission. In R. v. d. V. (Case VIII, Chart I) and W. H. (Case IX, Chart II) the S.O.C. fell during the attacks of haemolysis, and then rose again as the destruction of blood diminished. If one makes a chart of the bilirubin values of the serum and the deficiency of the S.O.C., joining up the top points, as has been done in the two figures, then one gets the impression that there is a connexion between the intensity of the blood destruction and the fall in the S.O.C., if it were permissible to draw a conclusion from this small number of observations.

In two cases of malaria also a deficiency in the S.O.C. was found during the attack (Table VI).

The question now arises: on what does the fall of the S.O.C. depend? I consider it improbable that faults of method have any influence worth mentioning on the results. It is true that in severe anaemias where there is a low percentage of haemoglobin, faults of technique in the method of examination are more important, but that does not explain abnormalities of 10 per cent. and more. Also, if that were the case, it would not be at all clear why the aberration from the normal should always be a fall, and never in some of the cases

a rise. And lastly, if that were the case, we should expect to find analogous aberrations in the secondary anaemias.

The only way in which this decrease of the S.O.C. can be explained seems to be that there is in these cases a substance derived from the haemoglobin in the red blood corpuscles, containing iron, but not possessing the power of normal haemoglobin to bind oxygen in its dissociated form. It is true one has not yet succeeded in showing this spectroscopically. One must, however, remember that methaemoglobin and sulphaemoglobin must be present in fairly strong concentra-

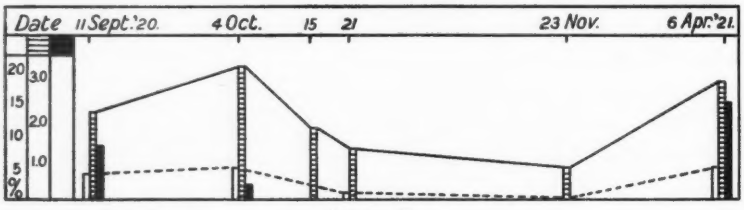


CHART I.

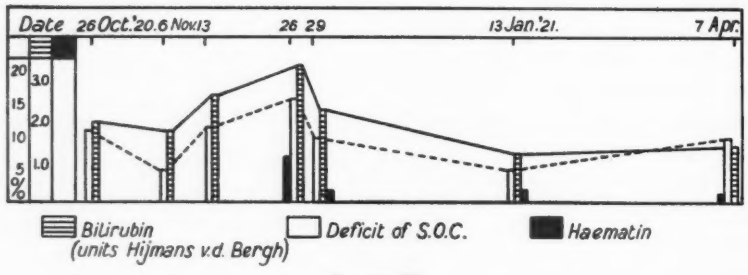


CHART II.

tion to be recognized in that way, and that haematin—even in fairly strong concentration—cannot be observed at all spectroscopically in the presence of relatively larger amounts of oxyhaemoglobin. Lastly, there has been nothing to prove that methaemoglobin, sulphaemoglobin, and haematin are the only iron-containing haemoglobin derivatives which may occur in the blood in pathological conditions. Possibly in such cases the blood may contain haemoglobin derivatives containing iron, but without any perceptible absorption in the visual spectrum, or with an absorption band falling inside the intense absorption area of a blood solution, and so not visible in the spectrum of this solution.

The drop in the S.O.C. spoken of here may thus quite well be due to intra-globular haemoglobin changes. The observations made in the two cases of malaria are specially interesting in this respect: the deficit was 6½ per cent. and 5½ per cent. respectively, more than can be attributed to faults of observation (the gas analyses and iron determination were in accordance with each other, and the amount of haemoglobin was slightly below the normal). In malaria one sees in the course of a few hours the infected blood corpuscles swelling and becoming pale, while at the same time intracorpuscular haematin is deposited in the form

of pigment, evidently formed from the haemoglobin by the parasite. Hence in an attack of malaria one has to do with an *intraglobular haematinaemia.*

The results obtained from the haemolytic anaemias are thus not in accordance with the present view that the specific oxygen capacity in all kinds of anaemia, including Addison's anaemia, keeps its normal value. This view is chiefly supported by the investigations of Butterfield (2) and by those of Masing and Siebeck (7), to which we must here devote a word or two.

Butterfield compared the light absorption and carbon-monoxide binding powers, and the amount of iron contained in the haemoglobin of some of his cases, and obtained constant proportions. By analogy he concluded that there would be a constant specific oxygen capacity. He examined the blood of one healthy person, one case of vitium cordis, one of hemiplegia, four cases of polycythaemia, one of pernicious anaemia, two of chlorosis, one of scurvy, and one of pseudo-leukaemia. His conclusion that in pernicious anaemia too the proportion between the light absorption, the oxygen binding power, and the iron content, remains the same, depends on *one* observation of *one* patient at a certain moment. Since clinical facts are lacking in Butterfield's work we do not know whether or not the patient was in a stage of remission or in a period of haemolysis. Hence his results do not enable us to come to a conclusion about pernicious anaemia in general. For the rest it is clear that by his methods Butterfield would have obtained normal values even if a very marked drop in the S.O.C. had taken place, as for example, if 25 per cent. of the blood-colouring matter had been changed into methaemoglobin. In making use of Peters's (8) method of examination I have found a S.O.C. of 300, quite apart from faults of observation, but Butterfield found by his methods the normal value of 400. In his procedure the carbon-monoxide absorption takes place *after reduction with hydrazine*, hence after methaemoglobin has been changed into reduced haemoglobin, he obtained artificially a gas binding power which the circulating blood did not possess. The same can be said of the presence of haematin. Whereas oxygen cannot be obtained from haematin either by potassium ferricyanide or by the pump, in Butterfield's method this colouring matter is first reduced to haemochromogen after which it takes up just as much carbon monoxide as an amount of haemoglobin containing the same amount of iron (Hüfner and Küster (9), Pregl (10)).

Even in cases with marked methaemoglobinaemia or haematinaemia the blood will, after reduction by hydrazine, have a normal carbon monoxide absorbing power. And so the experiments of Butterfield, however excellent in many respects, do not prove anything about the actual S.O.C. of the circulating blood.

Masing and Siebeck (7), who also believed in a constant S.O.C. in anaemias, obtained their results in the following way.

In a large number of cases, healthy persons as well as patients, the amount of iron per gramme of haemoglobin was determined, and an average taken; this was compared with an average of oxygen determinations (also per gramme of haemoglobin, spectroscopically determined), which returned a S.O.C. value of 397.

Hence the comparison is not made between the oxygen binding power and the iron content of every sample of blood, but the final result is obtained from two averages, each obtained from varying sources. Thus it is difficult in these results to express aberrations from the normal in individual cases. That such individual aberrations may be fairly large is evident from the fact that their iron values vary from 0·27–0·30 per cent. (difference of 10 per cent.), and their oxygen values from 113 to 120 c.c. per 100 grm. of haemoglobin (difference of 6 per cent.). So the observations of Masing and Siebeck do not compel us to believe in the existence of a normal S.O.C. in pernicious anaemia.

Leschke and Neufeld (11) found a normal S.O.C. in six cases of pernicious anaemia. They never found products of haemoglobin destruction present in washed red blood corpuscles. In one case the red blood corpuscles contained methaemoglobin; the ratio of O to Fe was in this case not 2 : 1, but 1·4 : 1 so that 30 per cent. of haemoglobin was changed into methaemoglobin.

Conclusions.

1. In normal persons values for the specific oxygen capacity of the haemoglobin were found similar to those of Peters, and in accordance with the conception that the maximal amount of oxygen taken up by haemoglobin is two atoms of oxygen to one atom of iron.

2. From the above we must not conclude that the S.O.C. in all healthy mammals is always 401; in seemingly quite healthy rabbits intraglobular sulphaemoglobinaemia occurs spontaneously, which causes a fall in the S.O.C.

3. In three cases of *autotoxic intraglobular sulphaemoglobinaemia* the S.O.C. of washed red blood corpuscles was found to be less than 401.

4. In cases of *secondary anaemia* the S.O.C. was unchanged.

5. In haemolytic processes—e. g. pernicious anaemia and malaria—the S.O.C. may drop in periods of blood destruction. In malaria this drop is probably due to an intraglobular haematinaemia. In pernicious anaemia the cause of the drop could not be spectroscopically demonstrated.

TABLE I. *Normal Persons.*

Name.	Oxygen Capacity c.c.	Iron Content mg.	Specific Oxygen Capacity.
1. B. v. B.	181·2	0·4500	*403*
2. H. P.	182·5	0·4589	*405*
3. A. B.	193·9	0·4820	*402*
4. C. V.	193·1	0·4806	*401*
5. J. R.	186·6	0·4696	*397*

TABLE II. *Intraglobular Sulphaemoglobinaemia.*

Name.	Diagnosis.	Oxygen Capacity c.c.	Iron Content mg.	Specfic Oxygen Capacity.	Deficit.
1. K. V., Dec., 1920	Hirschsprung's disease	180·4	0·5560	*324*	19 %
2. Ibid., Feb., 1921	„	178·6	0·4946	*361*	10 %
3. Mrs. S. D.	Retro-uterine haematocele	123·2	0·3380	*356*	11 %
4. Mrs. S.	Carcinoma mammae	159·1	0·5103	*312*	22 %

TABLE III. *Blood of Rabbits.*

Number.	Origin.	Number of Cases.	Sulphaemoglobin-spectrum.
7 rabbits	Medical clinic	1	Distinctly positive
		2	Distinctly positive
		3	Intense band, to be seen *in vivo*
		4	Trace
		5	Trace
		6	Negative
		7	Negative
5 rabbits	Pharm. Institute (Prof. Magnus)	8	Negative
		9	Negative
		10	Negative
		11	Very faint absorption
		12	Distinctly positive
8 rabbits	Bought on the market, instantly examined	13	Intense band, to be seen *in vivo*
		14	Intense band, to be seen *in vivo*
		15	Very faint absorption
		16	Very faint absorption
		17	Negative
		18	Negative
		19	Negative
		20	Negative
10 rabbits	Veterin. clinic (Prof. Blick)	21	Negative
		22	Negative
		23	Intense band, to be seen *in vivo*
		24	Negative
		25	Negative
		26	Distinctly positive
		27	Distinctly positive
		28	Distinctly positive
		29	Faint band
		30	Faint band
25 rabbits	Veterin. clinic (Prof. Wester)	31	Distinctly positive
		32–55	Negative

TABLE IV. *Secondary Anaemias.*

Name.	Diagnosis.	Serum.	Oxygen Capacity c.c.	Iron Content mg.	Specific Oxygen Capacity.
1. A. v. d. B.	Gastric ulcer	Bilirubin 0·4 haematin –	107·7	0·2678	*402*
2. Mrs. Sch.	Myxoedema	Bilirubin 0·35 haematin –	124·4	0·3101	*401*
3. Mrs. v. S.	Abortion	Bilirubin 0·3 haematin –	114·5	0·2898	*395*
4. G. G.	Cirrhosis of liver	Bilirubin 0·3 haematin –	155·0	0·3819	*406*
5. K. E.	Sepsis	Bilirubin very low haematin –	138·3	0·3437	*402*
6. C. H.	Late rickets	Bilirubin very low haematin –	108·4	0·2725	*398*
7. Mrs. H.	?	Bilirubin very low haematin –	68·8	0·1719	*400*

TABLE V. *Pernicious Anaemia.*

Name.	Diagnosis.	Serum.	Oxygen Capacity c.c.	Iron Content mg.	Specific Oxygen Capacity.	Deficit. %
1. J. M.	Pern. anaemia	Bilirubin 1·0 haematin + + +	75·0	0·2146	*350*	13
2. T. v. d. B.	Pern. anaemia	Bilirubin 1·15 haematin + + +	114·6	0·3144	*364*	9
3. Miss K. L.	Pern. anaemia	Bilirubin 1·6 haematin –	68·4	0·1897	*361*	10
4. Miss M.	Pern. anaemia	Bilirubin 0·4 haematin –	89·9	0·2223	*404*	0
5. B. E.	Pern. anaemia	Bilirubin 0·3 haematin –	82·7	0·2024	*409*	–2
6. C. H. Dr.	Pern. anaemia	Bilirubin 0·35 haematin –	135·9	0·3376	*402*	0
7. W. v. T.	Pern. anaemia 1st estim.	Bilirubin 1·35 haematin + +	56·8	0·1564	*364*	9
Ibid.	2nd estim.	Bilirubin 0·4 haematin –	135·1	0·3420	*395*	1
8. R. v. d. V.	Pern. anaemia 1st estim.	Bilirubin 2·15 haematin + + +	84·0	0·2202	*382*	5
Ibid.	2nd estim.	Bilirubin 2·9 haematin + +	120·2	0·3190	*377*	6
Ibid.	3rd estim.	Bilirubin 1·3 haematin –	145·2	0·3665	*396*	1
Ibid.	4th estim.	Bilirubin 0·8 haematin –	179·6	0·4455	*403*	0
Ibid.	5th estim.	Bilirubin 2·5 haematin + + +	82·8	0·2192	*378*	6
9. W. H.	Pern. anaemia 1st estim.	Bilirubin 2·0 haematin –	55·7	0·15635	*356*	11
Ibid.	2nd estim.	Bilirubin 1·75 haematin –	43·0	0·1136	*379*	5½
Ibid.	3rd estim.	Bilirubin 2·65 haematin +	40·2	0·1130	*355*	11
Ibid.	4th estim.	Bilirubin 3·4 haematin + +	32·7	0·0970	*337*	16
Ibid.	5th estim.	Bilirubin 2·3 haematin +	30·5	0·0850	*359*	10
Ibid.	6th estim.	Bilirubin 1·2 haematin +	95·5	0·2517	*380*	5
Ibid.	7th estim.	Bilirubin 1·55 haematin +	77·0	0·2150	*358*	10

TABLE VI. *Malarial Fever.*

Name.	Diagnosis.	Serum.	Oxygen Capacity c.c.	Iron Content mg.	Specific Oxygen Capacity.	Deficit. %
1. J. v. d. G.	Mal. fever (malignant)	Bilirubin 2·6 haematin +	159·2	0·4243	*375*	6½
2. G. v. V.	Mal. fever (tertian)	Bilirubin 0·5 haematin +	199·1	0·5219	*381*	5

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THE PULSE-RATE AND RANGE IN HEALTH AND DISEASE DURING CHILDHOOD[1]

By G. A. SUTHERLAND and JOHN McMICHAEL

It is a well-known fact that during sleep the pulse-rate is slower than during the waking hours. It has also been recognized that in children this variability in the pulse-rate may be very great. Feer (1) makes the statement that in childhood the pulse-rate during the day may be 10–40 beats faster than during sleep. He stresses the importance of counting the pulse in children while they are asleep and disregarding figures taken during the day.

It is generally accepted that during early life the heart-rate is more frequent than after puberty, but the tables of figures quoted in the books are of relatively little value owing to the marked variation which takes place in individual cases. In children a stable action of the heart has not been established, and many disturbing factors have an effect which is not seen in later years. It is thus very difficult in many cases to decide whether an increased frequency of the heart-rate is due to physiological or pathological causes, and this difficulty led us to investigate the physiological variations in the heart-rate in children, and the effects of disease on these variations. It is not necessary to make a distinction between heart-rate and pulse-rate because only very exceptionally (e. g. from extra-systoles) do they differ in childhood. The subjects of this investigation were from 2 to 12 years old—infants not being suitable for many reasons.

Normal Variation in Heart-rate.

There is a normal variation in the heart-rate between that of the sleeping and that of the waking hours amounting to more than 30 beats (see Table). The early morning readings were taken during deep sleep, while the afternoon rates were taken usually just after the mid-day meal, with the child still in bed, so that such extraneous factors as exertion and excitement were excluded. We observed, however, that getting the child up out of bed made very little difference to the afternoon pulse-rate after the first day up.

A closer analysis of this daily variation is shown in Fig. 1, which is a two-hourly pulse chart in a healthy girl of 11. During deep sleep the heart-rate approaches very closely to that present in adult life. On waking the child's heart-rate mounts up possibly by 10–15 beats, even although she is still resting quietly in bed. This may be assumed to be due to the influence of sensory

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impressions acting through the eyes and ears on the nervous centres controlling the heart. Later on in the day, as the child sits up in bed and takes the ordinary interest in her surroundings, the pulse rises still more. When she is up in the afternoon the rate reaches its greatest height and then falls again while in bed, reaching the minimum when the child has been asleep for an hour or two.

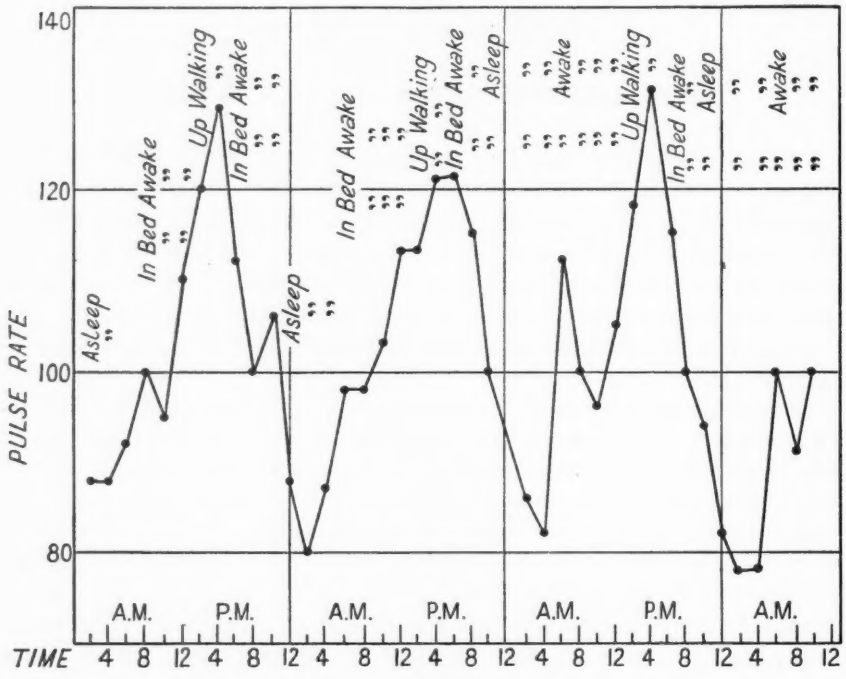


FIG. 1. Two-hourly pulse chart in a convalescent child with a note of the patient's activity at each reading.

Explanation of Normal Variation.

The mechanism of this reduction in pulse-rate during sleep is probably complicated. According to Klewitz (2) the average reduction in adults during sleep is 14·8 beats. This variation does not attract much attention and is probably explained as a result of diminished metabolism and slightly lowered temperature. Mackenzie, and later Lyon (3), have shown that the pulse-rate changes about 10 beats for each rise of one degree Fahrenheit. This is probably a direct temperature effect on the sino-auricular node, for experimental warming of the node in the excised heart increases the rate, independently, of course, of the cardiac nerves.

The slight diurnal range of temperature, however, does not explain the range of over 30 beats in the cardiac rate which is common in childhood. A range of this extent in adults is only seen in very nervous people. Kanner (4)

quotes the case of a woman aged 41, suffering from hysteria. The normal rate of the pulse was 99 by day and 71 during sleep, a range of 28 beats. It seems almost certain, therefore, that the explanation of the extreme variability of the pulse-rate in childhood lies in the unstable nervous system of the child. The 'normal' heart-rate is present only when the child is asleep and the nervous

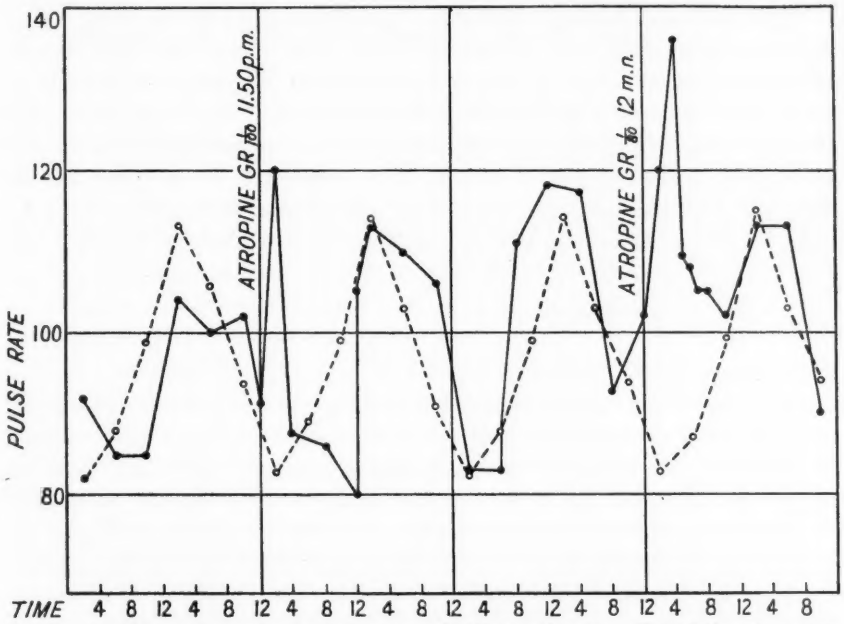


FIG 2. Effect of atropine on the nocturnal fall in pulse-rate. Dotted line shows the average daily pulse chart calculated from the preceding fifteen (apyrexial) days on this patient. Continuous line shows the actual rates at the times indicated on the days of the injections. Injections of atropine are seen to abolish the expected fall in pulse-rate at 1 a.m. The patient slept soundly on each occasion.

system is cut off from all outside stimuli. It is only under this condition that the unstable central nervous mechanism which controls the heart-rate via the vagus and sympathetic nerves is free from disturbance. When the child goes to sleep the heart-rate does not fall at once to its lowest level. Some time elapses before the effects of the stimulation of the nervous system during the waking hours have passed off. The lowest level of the heart-rate is reached between midnight and 4 a.m. It will be found that the maximum rate is reached between the hours of midday and 4 p.m. The nervous system is most thoroughly rested when the heart-rate is slowest in the early hours of the morning. It also reaches its maximum activity and excitability in the early afternoon when the pulse-rate reaches its maximum. We have also observed that when a child falls asleep in the early afternoon the pulse-rate falls, though not usually quite so low as the minimum nocturnal rate.

Fig. 2 shows the effect of atropine in abolishing the nocturnal fall in pulse-rate in spite of the fact that the patient remained sound asleep. The atropine

has disturbed the balanced action of the vago-sympathetic nerve-supply during sleep. The variation, then, is due in all probability to nervous influences.

Value of Normal Variation.

This nocturnal slowing is probably of great importance for the child. It is well known that quickening of the heart takes place at the expense of diastole, and the duration of systole is directly proportional to the number of heart beats per minute. According to Hürthle, with a pulse-rate of 50–78 per minute the absolute duration of systole is 33–37 per cent. of the entire heart period. This means that the heart under these conditions spends two-thirds of its time in rest. Sleep for the child thus becomes the great means of rest, not only to the body, but to the heart also. It is not merely the active limbs of the child, but also the active heart by day which calls for prolonged rest at night.

Instability of the Heart-rate in Nervous Children.

The diurnal variation in the heart-rate, i. e. the difference between the sleeping and the waking rates is much increased in children of a nervous temperament. On the other hand, this variation may be, and usually is, much less marked as regards the increase in rate during waking hours in the case of children of a dull phlegmatic temperament. The highly excitable child presents a difficult problem if he shows a heart-rate of, say, 140, without obvious cause.

Koplik (5) refers to such cases as follows: 'Some children without any physical signs except a neurasthenic hyper-excitable disposition show a rapid pulse-rate. The pulse-rate may be constantly high, 110–120, and during examination 140–160 without any real tachycardial attacks. These children have no other symptoms except that of hyper-neurasthenia and grow up as neurasthenics. Girls form a large percentage of such cases. In treatment attention is to be directed to the instability of the nervous system in these children and to the improvement of the general health.'

Dr. Koplik is describing a very familiar type of case, but he goes too far in labelling these children as neurasthenics. The hyper-excitable child is not necessarily a neurasthenic, but is the best example we have of this extreme diurnal variation in the cardiac rate. It is well known that rheumatic infection is apt to affect the nervous system and render a child excitable, jumpy, and nervous. It will be found that rheumatic children usually show a wide range in the cardiac rates during sleeping and waking hours.

A physician examining one of these children may find it impossible to say at once how far the action of the heart is disturbed, and whether the rapid rate is physiological or pathological. The doctor's presence is probably the exciting cause of the rapid rate, and it will continue as long as he remains. The crucial test in the diagnosis of these cases is the counting of the pulse-rate while the

child is asleep. Whether it has been 140 or 150 during the day it will be found to fall under 100 during sleep. If on the other hand there is no such fall in the pulse-rate during sleep one will do well to look out for some other cause such as local disease, or toxaemia, or heart trouble. The condition known as paroxysmal tachycardia is easily distinguished from the rapid heart of nervous children by the fact that in attacks of the former the tachycardia begins and ends abruptly and is continuous at the same rate throughout the whole attack.

Effect of Pyrexia on Normal Variation.

As a rule in pyrexial conditions the pulse-rate is increased and varies with the temperature. As stated above, the increase in adults is about 10 beats for a rise of one degree Fahrenheit. In childhood similar changes occur in the heart-rate under conditions of pyrexia, and differ only in the fact that the increase in rate is more pronounced.

When we consider the effect of pyrexia on the pulse chart of a child we find that it may take one of two main forms.

(*a*) The pulse-rate may show a fluctuation within a certain range, which however is entirely different from that seen in the healthy child. For example, with a temperature fluctuating between 101° and 103° we may find a pulse-rate varying from 130–150. This variation accompanies the fluctuation in temperature, and is quite independent of nervous influences.

(*b*) With a high-continued fever, such as occurs in lobar pneumonia, the nocturnal slowing is completely abolished and the pulse-rate will continue at a uniform high rate, day and night, with little or no fluctuation.

In pyrexial conditions, therefore, the influence of the cardiac nerves is completely lost and the temperature becomes the controlling factor of the activity of the sinus node.

Case 1. A. C., aged 8 years. History of headache and shivering three days before admission. The following day she was feverish and developed a pain in the left side of the chest. No previous history of cough.

On admission, temp. 103°; pulse 116; respirations 36. She was flushed and ill.

Tubular breathing, with some crepitations, was audible over the left lower lobe. The temperature settled slowly by lysis and the lung signs cleared up completely. The diagnosis was lobar pneumonia.

The chart (Fig. 3) shows that the pulse-rate was maintained at 108–116 in the first twenty-four hours with little or no nocturnal fall in rate. After this as the temperature settled, the nocturnal slowing was gradually re-established. It is to be specially noted that, with a normal temperature, the afternoon pulse-rate rises almost to the level maintained during the acute fever.

The return of this diurnal variation after a febrile illness may be regarded, *qua* heart, as a good sign. Normally the cardiac rate is regulated by a vago-sympathetic balanced action which is found during childhood in an undisturbed state only during sleep. This vago-sympathetic control may be abolished in illness from various causes such as heat, toxaemia, blood infection, carditis, &c.,

acting directly on the sino-auricular node. The pacemaker of the heart passes temporarily under the stimulating influence of pyrexia or toxins, and the increase of rate which follows will persist day and night as long as one or more of these factors is present. The return of vago-sympathetic control is shown by the return of the diurnal variation. In pyrexial disease this will not occur so long as the feverish state lasts. In toxic disease it will not occur as long as the toxins

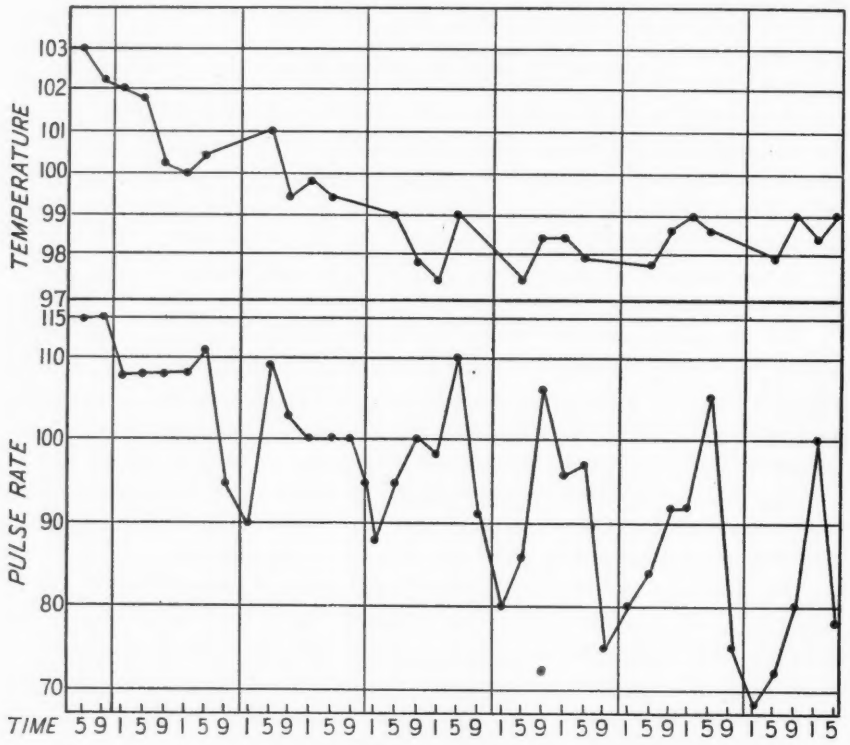


FIG. 3. Case of pneumonia terminating by lysis and showing gradual restoration of the normal diurnal variation.

are acting on the heart. So we are justified in viewing the return of this diurnal variation as a favourable sign. It may be regarded as an indication that the heart has not suffered so far as the sino-auricular node is concerned. This node is a very sensitive part of the heart, and there is seldom any toxic or inflammatory change in the myocardium without some involvement of the node during the active stage.

Heart-rate in Rheumatic Carditis.

That a rapid pulse may be the only sign of activity in a case of rheumatic carditis has long been recognized. Poynton (6) indicates that carditis *per se* is an afebrile condition. It may only be diagnosed by acceleration of the pulse-

rate. Hutchison (7) has emphasized the importance of pulse charts, and this was also stressed by Bourne (8) in a recent paper. Bourne states that 'The spikiness of the pulse-rate during activity is even more striking than is the irregularity of the temperature curve. . . . In most cases of active carditis the pulse-rate varies very greatly within a few days, producing a curve like a silhouette of some mountain range. With quiescence the undulations become milder and ultimately vanish.' He gives a chart showing these spiky undulations with a heart-rate varying each day from 80 to 120 per minute. We submit that, according to the normal standards which we have indicated above, *the daily fall of the pulse-rate to 80 indicates a normal state of affairs*, and a pulse chart of this type is an indication that no active condition is present.

It is of the utmost importance to be able to decide whether a rapid pulse in a rheumatic child is physiological or pathological. The presence of a rapid pulse in rheumatic children who have presented evidence of carditis is often regarded seriously. A prognosis which is unnecessarily gloomy may be given, and the child may be kept in bed for an unwarrantable time in the attempt to reduce a tachycardia which is physiological. To distinguish the physiological from the pathological it is absolutely essential to count the pulse during sleep, especially in the early morning when the child has been asleep a few hours. When the tachycardia is physiological it will be found that the heart which was beating at 120 by day has changed to a rate of 70–90 during sleep. In rheumatic children the diurnal variation in heart-rate is usually very pronounced because of the nervous excitability accompanying that disease.

When the tachycardia is due to a definite organic rheumatic carditis the pulse-rate *continues rapid day and night.* Rheumatic infection of the heart has been present and persists as regards an over activity or excitability of the sino-auricular node which regulates the heart-rate. In these cases the diurnal variation in the heart-rate disappears entirely or is very slight. The cardiac rate remains rapid and cannot be slowed or altered by any amount of rest.

Case 2 illustrates the establishment of carditis (see Fig. 4).

V. R., aged 12 years. Admitted with acute sero-fibrinous pericarditis. There was a history of joint pains for about eight weeks before admission.

The heart was enlarged and very rapid, but under the usual salicylate treatment he made a very good recovery from the pericarditis. At the end of five weeks (May 20) the temperature chart was steady and normal and the pulse-rate showed a daily range of 75 to 110 which was considered normal and satisfactory. Unfortunately he relapsed. A few days later the pulse-rate began to 'step up', and soon the temperature began to rise. Coincidently a rheumatic erythema appeared on the trunk.

After a few fluctuations the temperature settled down to normal at the end of a week, but the *pulse-rate remained persistently rapid,* about 120 to 130 per minute, day and night.

For the next three weeks that the patient remained in hospital the temperature was practically normal, but the pulse-rate remained steady at this 120 level all the time.

Patient was later discharged to a convalescent home still suffering from active carditis.

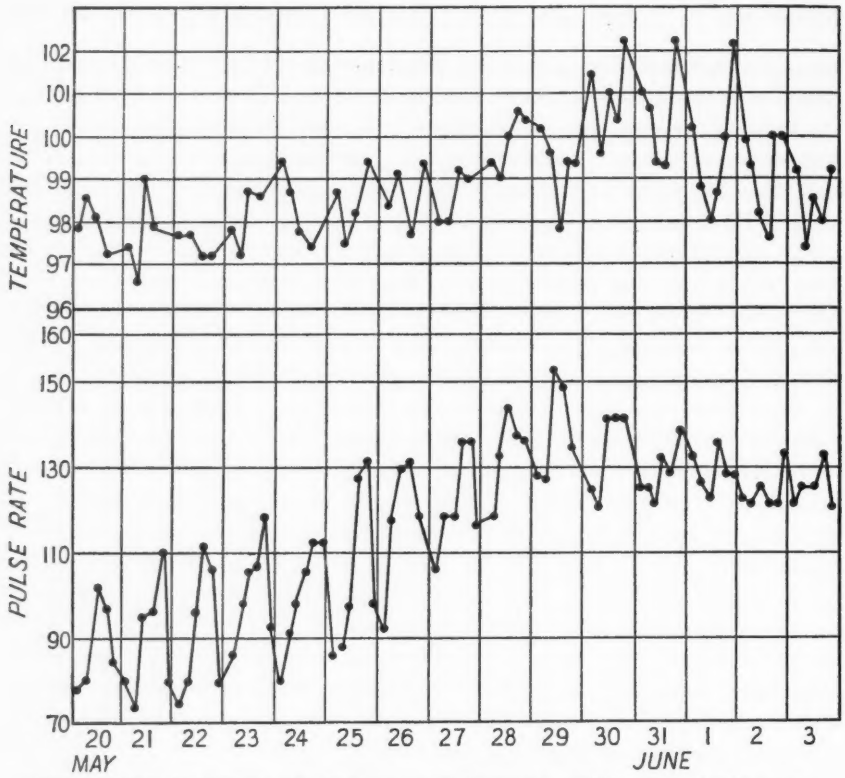


FIG. 4. Chart to illustrate the development of rheumatic carditis. Four-hourly chart. Readings taken 1, 5, 9 a.m. and 1, 5, 9 p.m.

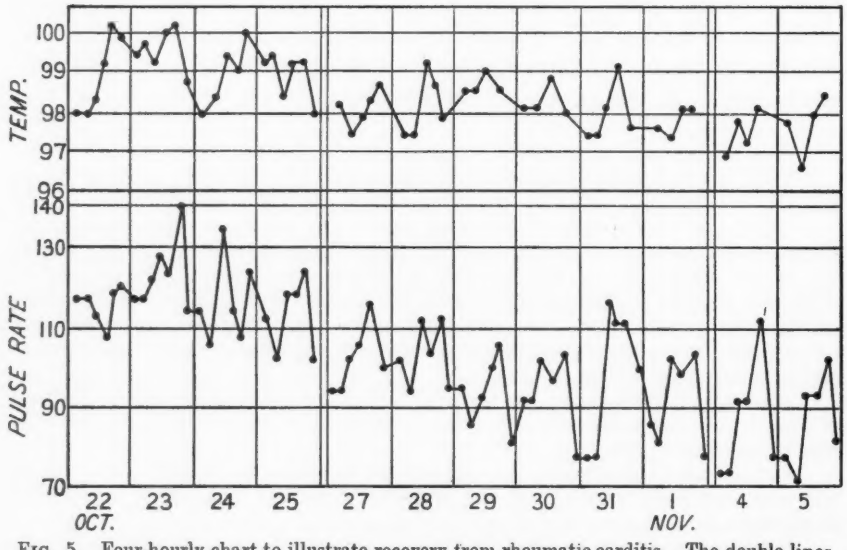


FIG. 5. Four-hourly chart to illustrate recovery from rheumatic carditis. The double lines indicate the omission of a day or two to make the chart a more convenient size.

Case 3 illustrates recovery from rheumatic carditis (Fig. 5).

B. C., aged 8 years. Admitted October 17, 1928.

The child had had an attack of acute articular rheumatism in July 1928. She was kept in bed until September 20. Since then she had had persistent twitching, mainly affecting the right side, and had become very pale and breathless.

On admission the heart-rate was very rapid, 110–150, with very numerous auricular extra-systoles. The apex beat was ¾-inch external to the nipple line, and systolic and diastolic murmurs were noted at the mitral area. She also had slight chorea.

Progress. Premature beats were present for two days, and then disappeared entirely.

October 22. Apex beat now ½-inch external to nipple line and pulse-rate 110–120, with no nocturnal fall.

In the next two days the temperature had risen a little and the pulse-rate touched 140 per minute.

Thereafter the pulse-rate began to improve. On October 29 it had reached a range of 88–108. Steady improvement continued until on November 5 the range was 72–106. Progress was uninterrupted. She was allowed up on November 14 for half an hour, and gradually this was increased, and the child was sent home on November 30 with no active symptoms and a normal pulse-rate and range.

The persistently rapid heart-rate demonstrated in these charts is pathological and is due to rheumatic infection of the sino-auricular node.

The recognition of the physiological and pathological types of tachycardia in a rheumatic child is also important from the point of view of treatment. Rest in bed is an important part of the treatment of active carditis, and frequently the duration of such rest is determined by the state of the heart-rate. If the rapid heart action is merely of the physiological variety, as tested by its slowing down at night, it is difficult to see what benefit or change of any kind is to follow from prolonged rest. A child in health suffers from prolonged rest in bed by the cutting off of all normal activities. A quiet restful day is not of so much importance to him as a quiet restful night. His sleep will probably be better if he has been up and about during the day. The heart will probably be more rested during the sounder sleep. If the presence of active carditis has been settled in the negative by the presence of this diurnal variation the child may be allowed to be up and about. If on the other hand the presence of active carditis is determined by the absence of this diurnal variation, then rest and more special treatment are called for.

The appearance of the signs of congestive heart failure in paroxysmal tachycardia is well known. The longer the attack lasts the worse do they become, because the heart gets no rest. To a less degree, the same thing happens in the persistently rapid heart of rheumatic carditis. When the heart has continued at this rapid rate day and night for weeks the already damaged myocardium becomes exhausted. We have repeatedly observed this in cases which were resistant to treatment by digitalis on account of vomiting. Even though these patients were resting in bed and there were no signs of fresh

rheumatic infection, at the end of a few weeks the liver slowly enlarged and oedema of the dependent parts appeared. If the heart can be slowed by digitalis, as it can be in many of these cases (9), the myocardium gets its period of rest and cardiac failure can be prevented or improved if it has already appeared. The return of the normal diurnal variation in the heart-rate is the most favourable sign that one can look for in these cases of rheumatic carditis.

Conclusions.

1. In healthy children the pulse-rate shows a diurnal variation, the afternoon rate being on an average 34 beats per minute faster than the early morning rate during sleep.

2. This variation is due to nervous influences and is most pronounced in children of a nervous and excitable temperament and in rheumatic children.

Case.	Age.	Disease.	Daily average minimum 1–5 a.m.	Daily average maximum 1–5 p.m.	Range.	No. of days observed.
J. B.	6	Pneumonia	80	126	46	20
E. B.	9	Purpura	75	117	42	12
J. C.	5	Haemorrhagic nephritis	80	103	23	20
D. C.	11	Pneumonia	74	95	21	6
A. C.	7	Pneumonia	74	101	27	8
S. F.	5	Chorea	84	122	38	16
K. H.	6	Rheumatism	71	107	36	18
A. H.	3	Cervical lymphadenitis	81	120	39	9
M. L.	11	Subacute rheumatism	66	106	40	6
D. M.	2	Asthma	73	107	34	8
D. N.	11	Rheumatism	64	102	38	12
V. P.	6	Haemorrhagic nephritis	72	100	28	13
H. S.	9	Pneumonia	80	104	24	5
J. S.	6	Pneumonia	72	99	27	7
L. T.	8	Pneumonia	65	103	38	4
P. B.	7	Fibroid lung	79	111	32	19
H. B.	3	Asthma	82	121	39	15
F. J.	8	Subacute rheumatism	66	101	35	10
K. C.	5	Subacute rheumatism	79	109	30	7
J. A.	6	Spleno-hepatomegaly	72	109	37	11
B. H.	5	Jaundice	78	112	34	11
L. M.	7	Nervous tachycardia	76	121	45	14
Q. P.	6	Fibroid lung	67	111	44	13
G. A.	8	Tonsillitis	63	96	33	7
R. T.	8	Pneumonia	77	108	31	7
K. S.	7	Fibroid lung	68	106	38	8
L. A.	12	Subacute rheumatism	70	98	28	12
C. W.	10	Fibroid lung	64	101	37	19
P. M.	4	Catarrhal jaundice	70	101	31	3
	10	Acute rheumatism	66	90	24	8
		30 Children average	73	107	34	328 days

Table showing the average daily minimum and maximum pulse-rates estimated from 328 daily readings in 30 children. They were taken during convalescence and the children had no pyrexia and no heart trouble.

3. In pyrexial conditions the diurnal variation disappears and is replaced by a pulse-rate dependent on the rise in temperature.

4. Abolition of the nocturnal slowing and a persistently rapid rate may be the only sign of active rheumatic carditis. The return of the diurnal variation is a healthy sign.

5. The presence of the diurnal variation in health, its disappearance in many diseases, and its return in convalescence call for further study.

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LATENT TUBERCULOUS LESIONS IN THE LUNGS AS DETERMINED BY ROENTGENOLOGICAL AND PATHOLOGICAL INVESTIGATION [1]

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With Plates 18 to 26

Introduction.

The frequency with which healed tuberculous lesions of the lungs occur in patients dying from causes other than tuberculosis was recognized as long ago as 1689, when Morton (9), published his 'Phthisiologia', more than two centuries before Naegeli (10) showed that pulmonary tuberculosis was practically universal amongst civilized races, and that recovery frequently occurred without the lesions being recognized during life. Although from time to time much has been written on this subject, the true significance of healed and latent lesions has not always received the recognition it merits.

More recently the anatomical features have been fully described by Opie (12 and 13), who defines a latent tuberculous lesion as a pathological process which, though still active, produces symptoms not recognizable by the patient, or signs that cannot be detected by the physician using ordinary clinical methods. According to their site, three main varieties are described by him:

(1) Focal nodules, varying in size from those barely recognizable macroscopically up to lesions 2–3 cm. diameter, scattered irregularly throughout the lungs, most frequently at the periphery.

These were present in 98 per cent. of white and 92 per cent. of coloured subjects.

(2) Similar areas of caseation or calcification in the tracheobronchial lymph nodes, which in 99 per cent. of cases were shown to be secondary to focal nodules of the first variety.

(3) Changes at the apex—fibrous scars, caseous or calcified lesions—which were demonstrated in 1 in 5 adults dying from causes other than tuberculosis. Attention was also drawn to the great frequency with which pathological changes were found in the apical pleura, but in which evidence of a tuberculous origin was less certain, or only indirect.

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In a more recent paper the same author (14) adduced evidence to show that the focal and lymph node lesions were the result of a first infection sustained during childhood, and that the apical lesions were caused by a second and independent infection during adolescence or adult life, and simulated in many respects the features of an experimental re-infection seen in animals.

For reasons to be discussed later the recognition of such pathological changes during life is of fundamental importance. Since, however, such lesions rarely manifest themselves by either constitutional disturbance in the patient or by physical signs, recourse must be had to auxiliary methods of diagnosis. Whereas in infancy information may be derived from the tuberculin reaction, in adults reliance must be chiefly on roentgenographic investigation. Hetherington (2) has recently investigated a large number of school children by means of routine radiograms and tuberculin tests, and found that latent tuberculous lesions of the lungs or tracheobronchial lymph nodes frequently existed in the complete absence of malnutrition or cachexia; a proportion of such cases did eventually manifest progressive disease.

The present investigation was undertaken with the object of correlating the roentgenological appearance of these lesions with the results of dissection of the lungs at autopsy. For this and similar purposes an X-ray apparatus was installed in the mortuary of the Philadelphia General Hospital.

Method.

Radiograms were taken first of the thorax of the cadaver, and then, where possible, of the intact lungs and trachea outside the body, after distension with air approximately to the volume occupied by them in full inspiration during life. This was followed by a careful dissection of the lungs in each case. In a few instances we were fortunate in having an X-ray of the chest taken shortly before death. Cases were chosen, as far as possible, where death was not associated with gross pulmonary disease, tuberculous or otherwise. Since a number of the cases that came to autopsy died shortly after admission, it was unavoidable that in some of those investigated, gross pathological changes were subsequently discovered, and these will be discounted in the description of healed and latent lesions. Only adults were used, and forty cases were investigated, in four of which one or other radiogram was unsuccessful and too poor to read.

It was early appreciated that such a study as this presented problems very different from those encountered in the radiographic investigation of the thorax during life. Whilst the immobility of the subject and the absence of vibration from cardiac activity, the importance of which was fully discussed by McPhedran and Weyl (7), at once simplified matters to the extent that a lower voltage and current with a relatively longer exposure could be used, certain difficulties peculiar to the lifeless body were encountered. Some of these, due to inherent differences between the living and the dead subject, are such as will not readily be overcome, whilst others will no doubt disappear with further development and improvement of the method and apparatus specially adapted to this par-

ticular problem. While some of the limitations to this study will be pointed out later in the paper, some of the difficulties may now be referred to.

The bodies used were mainly those of old individuals of either sex, many of whom died from cardiovascular disease which had resulted in considerable oedema and congestion, particularly in the postero-inferior parts of the lungs. Such congestion and stasis of the pulmonary circulation was especially frequent in many of the cases who had been lying on their backs for long periods of time before their death. Moreover, many of the bodies had been lying for some hours—occasionally for two to three days—on their backs in the ice chamber, and this frequently resulted in post-mortem hypostasis, both in the lungs and in the tissues of the thoracic wall. As will be pointed out later, fluid may produce opacities of considerable density in the X-ray films, and hence mottled shadows of varying density that are not usually seen in similar radiograms taken during life were frequently encountered, especially in the medial and inferior parts of the lung fields. For these reasons no strict comparison can be made between the roentgenograms taken during life and those taken after death, and in the latter case appearances may sometimes be misleading and deceptive. Furthermore, the thorax after death is practically in a position of expiration, and thus there is generally insufficient pulmonary aeration; this, together with the other factors to which reference has already been made, accounts for the fact that radiographic details of normal lung structure are frequently less clearly defined after death than during life, when the exposure is made at the height of full inspiration and with the subject in the upright posture. As there was no means of suspending the body, the radiogram had to be taken in the prone position. As a result, the inactive diaphragm was generally at a higher level than in life, and the resulting compression further diminished the pulmonary aeration. The prone position was found preferable, since in this way it was possible for the shoulder-blades to fall forwards and outwards, and sufficient flexion of the head and neck could be obtained to increase appreciably the intervals between the upper ribs. A further difficulty, not readily overcome, was the stiffness of the body and rigidity of the thoracic and cervical muscles. Difficulty in changing plates and maintaining the position of the cadaver did not permit the taking of regular oblique views. For similar reasons, stereoscopic films could not be obtained, and this further limited the amount of information that could thus have resulted. The object of this preliminary investigation, however, was to get some general idea of the size, nature, and position of relatively small lesions which could give unmistakable shadows in the radiogram, and in this paper it is hoped to point out the limitations and indicate the possibilities of the method.

All exposures were made with the tube at a distance of 3 ft. from the body or specimen.

Lesions as seen in Radiograms of Excised Lungs.

In X-raying the thorax during life, approach to the ideal state of affairs obtained when the inflated lungs are radiographed outside the body is sought

by removing as far as possible the obscuring effects of the bony structures of the thoracic wall. For this reason it may be profitable to review first the essential appearances of the various pathological changes encountered in the radiogram of excised lungs. This study had the added advantage of being a very reliable guide to both the normal anatomical and pathological architecture of the lung.

The importance of aeration was here well illustrated. The greater the aeration, the greater the amount of fine detail shown in the film. For with increasing distension with air there is increasing contrast not only between parenchyma and bronchial and vascular trunks, but also between pathological lesions and normal lung structures. When the collapsed lung is X-rayed, the whole lung field shows a shadow of a homogeneous density with little differentiation between vascular and bronchial trunks and the remaining lung tissue. Under such conditions, the only lesions distinguishable are densely calcified nodes over 0·75 cm. in diameter. Most of the other lesions, whether due to fibrosis, caseation, congestion, or oedema are only poorly differentiated, if at all. When considerably over-distended, the finer bronchi (up to the 3rd and 4th degree) can be recognized, and even fine fibrous strands can be identified. In such lungs normal tracheobronchial lymph nodes over 0·5 cm. diameter are distinctly outlined as light homogeneous shadows. With a distension approximately equal to that occupied during full inspiration in life, there are few pathological lesions that will escape detection. The terminal bronchioles occupying the peripheral quarters of the lung fields cannot be identified.

As McPhedran (6) has shown, the shadows thrown by normal lymphadenoid tissue at the hilum have the same density as the rest of the lung tissue and cannot, therefore, be differentiated under normal conditions of aeration.

Apart from the effects of difference in aeration, the prominence of the vascular and bronchial trunks varied with several circumstances. They were generally more prominent in older individuals, and this was particularly so where calcification of the cartilages occurred as far down as the bronchi of medium size (Case 23, Pl. 18, Fig. 1). In two cases where the pulmonary artery and its branches were occupied by an ante-mortem clot the trunk markings were particularly prominent. The shadows cast by the bronchial and arterial trunks were unduly conspicuous and wide in cases of moderate congestion or oedema, especially in those dying of heart disease with right-sided failure. Prominence of these shadows was also observed in bronchitis when the bronchi contained excessive fluid. In no case where the markings of these trunks were exaggerated was there any obvious macroscopic increase of the peribronchial connective tissue. It is important to realize that during life, as McPhedran and Weyl (7) have shown, other factors, such as diminished pulmonary elasticity with consequent reduction in cardiac vibration, tend to increase the prominence of these shadows.

In many films the effect of vascular stasis is well seen, for congestion, even of moderate degree, results in considerable mottling, particularly in the medial aspects and bases of the lungs, often increasing in density towards the hila. With

increasing pulmonary congestion or extensive oedema, a diffuse homogeneous density may result, obscuring all lesions, including calcified nodes of considerable size. For similar reasons a pulmonary infarct (Case 12, Pl. 18, Fig. 2) throws a densely homogeneous shadow with a sharply defined outline. Moreover, such pathological changes prevent proper inflation of the lungs.

The relative frequency with which the lesions under discussion are seen in roentgenograms is summarized in Tables I, II, and III.

The commonest of all lesions was a fibrous thickening of the pleura, often associated with fibrous adhesions to the chest wall. When this pleural lesion is very thin—under 1 mm. in thickness—it is generally not possible to differentiate it from the remaining lung structure unless it lies in a plane parallel to the direction of the rays, in which case it appears as a thin opacity along the margin of the lung fields (Pl. 19, Fig. 3). When such fibrosis is thicker than 1 mm. and lies in a plane at right angles to the direction of the rays, it appears as a diffuse stippling of light density in the lung field, which, without stereoscopic plates, cannot be distinguished from fibrosis or pneumonic infiltration of the lung parenchyma. A simple acute fibrinous pleurisy does not give rise to any recognizable opacity. Obliteration of an interlobar fissure by any but the finest fibrous adhesions results in a linear shadow between the lobes (Pl. 20, Fig. 4).

Within the lung substance, the pathological changes most often encountered were congestion, oedema, pneumonic infiltration, fibrosis, caseation, and calcification. To the first two of these reference has already been made. Acute pneumonic infiltration, whether tuberculous or otherwise, always produced shadows whose density varied directly with the extent of the lung involved. When affecting small isolated areas up to 1 cm. diameter, as in early cases, they produced a light stippled density. As these areas coalesced, so a mottled shadow of greater density resulted; when a larger portion of lung was involved, it produced a diffuse homogeneous opacity similar to that seen in oedema or infarction.

In Case 19 (Pl. 20, Fig. 4), where death resulted from generalized tuberculosis, the lungs showed discrete lesions of two kinds. Scattered throughout the lung substance in an irregular manner were numerous miliary and submiliary grey granulomatous tubercles up to 3 mm. diameter, and larger discrete broncho-pneumonic nodules having a trefoil arrangement along the distribution of the smaller bronchioles. Except that the broncho-pneumonic areas were apt to throw larger shadows, there was no other way of distinguishing these two lesions. In an adult negro (Case 34) dying from miliary tuberculosis, the cut sections of the lobes were studded with firm, discrete, granulomatous lesions varying in size from a pin-point to nodules measuring 1·5 cm. across. The radiogram of the excised lungs in this case (Pl. 21, Fig. 5) showed numerous conglomerating shadows, differing only from similar shadows cast by broncho-pneumonic nodules in that their centres were of heavier density.

Fibrosis met with in our cases was as a rule limited in size to a small area, generally of the lung apex (Pl. 22, Fig. 6). The resulting appearance of the radiogram varied with the size and density of the lesion. When involving an area less

than 0·5 cm. across, it did not throw a shadow readily differentiated from the rest of the lung parenchyma. When of greater size and with the strands not too compact, the resulting shadow consisted of a stippling or mottling of light density, and could not be distinguished from thickened pleura when X-rayed in the horizontal plane. With more compact fibrous lesions, or those of cartilaginous consistency, the resulting opacity was of medium density, homogeneous, and ill-defined; only when infiltrated with calcium did it throw a very dense shadow (Pl. 23, Fig. 7).

Calcified lesions gave shadows of the greatest density and as a rule most sharply circumscribed. When at the periphery of the lung field, nodules of 1 mm. diameter could be detected in the films where they were not obscured by other pathological changes. The minute and ill-defined opacities resulting from these must be distinguished from thickenings seen at the angles where trunk markings branch. The caseous lesions met with in this series were generally of a quiescent or latent nature, discrete and circumscribed, and usually under 1·5 cm. diameter. These all gave shadows only slightly less opaque and sharply defined than the frankly calcareous lesions. As Opie (16) has shown, caseous lesions of long standing have a considerable amount of calcium recognizable by microscopic and chemical means.

In three cases where ulcerative tuberculosis was found *post mortem*, an opportunity was afforded of noting the appearance of cavities. These showed that frequently a cavity of considerable size, when surrounded by extensive areas of consolidation—as is often the case—may be represented in the films as an area of lighter density very much smaller than the actual cavity itself. The more normal the surrounding lung tissue, the more accurately will the cavity be represented in the radiograms. Such films have also shown (as in the base of the right upper lobe of Case 19) that a small area of emphysematous lung tissue, surrounded by caseous consolidation, may give an appearance closely simulating true cavitation (Pl. 20, Fig. 4).

With regard to the radiographic appearances of pathological changes in the hilum lymph nodes, these have been thoroughly studied by McPhedran (6), and his findings have been fully confirmed here. Calcification, frequently undetected by dissection, was readily demonstrated in the films. Other changes, whether due to fibrosis or acute inflammatory swelling, did not give rise to shadows that could be differentiated from the remaining lung structure, except when the nodes reached considerable dimensions. Pl. 21, Fig. 5 shows the film from an adult negro who died of the 'childhood' variety of acute pulmonary tuberculosis. The tracheobronchial nodes formed a large mass, in which the greatest diameter of some of the larger nodes measured 7 cm. Only in the lower part of the mass was there a limited amount of necrosis; the greater portion of the periphery was firm and of cartilaginous consistency, which microscopically showed caseation surrounded by dense fibrosis. There was no evidence of calcareous infiltration. In the radiogram of the excised lungs this mass of lymph nodes is seen as a well-defined, homogeneous, saddle-shaped shadow of similar density to the other con-

solidated areas in the lung field. The shadow cast by these nodes in the films corresponded in size to the mass found at autopsy.

Collections of pigmented lymphadenoid tissue up to 0·5 cm. diameter could frequently be seen at autopsy lying adjacent to the bronchi as far as 6 or 7 cm. away from the hilum, and similar collections were often seen beneath the pleura, especially on the inner aspects of the lungs. These could not be differentiated from normal lung tissue in the radiograms, except when they were the seat of calcification, as was often the case in the parabronchial lymphadenoid tissue.

It is interesting at this point to compare briefly the shadows cast by other lesions. Non-tuberculous fibrosis produces a homogeneous shadow similar to, but less dense than, that resulting from an infarct. Secondary new growth (Pl. 24, Fig. 8) produced a characteristic picture: numerous overlapping, well-defined, circular shadows of moderate density, occasionally having lighter areas in their centres, due to necrosis and liquefaction. A pulmonary phlebolith was met with in only one instance, and produced a small density 2 mm. in diameter, indistinguishable from similar shadows cast by small calcified foci of similar size.

Lesions seen in Radiograms of Thorax taken after Death.

The relative frequency with which lesions found at autopsy were revealed in the radiograms of the thorax is summarized in Tables I, II, and III. At the outset it must be emphasized that, in the case of lesions producing lighter shadows, a much smaller number will be seen in the average roentgenograms of the cadaver than in those taken from the living subject. With lesions producing greater densities (as with calcified nodes), the picture obtained will very closely resemble that in the living subject.

To some of the factors reducing the frequency with which small lesions are seen in chest plates reference may briefly be made. These may be either anatomical or pathological. Of the former, the ribs are most often a source of obstruction. In most patients a rib will hide all shadows except those resulting from calcified lesions over 0·4 cm. diameter. By means of stereoscopic films or several films taken at different levels it is possible, by the rays striking the lesions at different angles, to show a shadow above or below a rib in one or other of the films. The greatest difficulty was encountered at the apex, where a large number of relatively small lesions of considerable significance occur. Owing to the width of the first rib and its oblique position, the first intercostal space is very narrow. Further, owing to its short length and great curvature, the rib forms a bony rim covering the greater part of the summit of the upper lobe, which difficulty cannot be readily overcome by taking plates at different angles. In most films taken with the tube centred over the upper dorsal vertebrae the first and second ribs completely overlap. By having the tube about 3 feet above the cadaver (lying prone) and 1½ feet anterior to the head, and by so tilting either the tube or the body that the rays were directed towards the second dorsal spine at an angle of 60° with the horizontal, a considerable interval between the first and

second ribs can be brought to view. In such a film the intervals between the second and third and third and fourth ribs were relatively narrow. These could best be brought to view by centring the tube vertically over the second dorsal vertebra. By taking three exposures of the apices at varying angles, a greater extent of lung tissue uncovered by ribs could be brought into view than by a single exposure.

The sternum, mediastinum, and transverse processes of vertebrae proved very considerable obstacles in antero-posterior exposures. These covered up at least the inner fifth of each lung, and on the left side this hidden area was greatly increased by the heart. In the supraclavicular region almost a third of the lung substance was hidden, and this was often increased by the presence of thick and rigid neck muscles. The bases of the lungs were covered by upper abdominal contents to an extent dependent upon the height of the diaphragm. Under the conditions of this investigation, it was often as high as the seventh rib on the right side. On this side the opacity of the liver was sufficient to hide all pulmonary densities. At the left base much depends upon the contents of the stomach; under average conditions no lesions except calcified nodes of 0·5 cm. diameter or more can be recognized. Of pathological lesions, the greatest obscuring effects are produced by fluid, whether within the lung, the pleural space, or in the chest wall as oedema. Transudation fluid anywhere is generally opaque, and whether it exists as a pleural effusion or a pulmonary oedema, the resulting homogeneous opacity is of similar density.

For the purpose of correlating autopsy findings with the appearances in chest films, only thirty-six cases are available, since in four instances the films here are too poor to allow of adequate interpretation.

Pleural Lesions.

These were very frequently encountered at autopsy (see Table I). Simple puckering without obvious macroscopic thickening was not included in this study. For the purpose of this paper the term pulmonary apex is used to describe the upper 4 cm. of the upper lobe. Of the 36 cases, the apex alone of one or both lungs was involved in 17, and the apex together with other areas in 9 cases. In the first group evidence of pleural lesion was seen in the films of excised lungs in 16 instances, but in chest plates in only 2. In the second group, in 8 such evidence could be recognized in films of excised lungs and 3 in chest plates. Of 26 cases showing apical pleural lesions, 20 were in white (87 per cent.) and 6 in coloured adults (40 per cent.); of 19 males 13, and of 17 females 13, respectively, showed the lesions. In half the instances pathological change was limited strictly to the pleura, and in the other half there was also extension to the underlying parenchyma. The lesion was bilateral in 13 cases, on the right side in 8, and on the left side in 5.

The reasons for the infrequency with which these pleural changes are seen in chest plates are not far to seek. In 11 of these autopsies the thickening

was limited to the upper 3 cm. of the upper lobe, or to its inner border, and was thus covered either by the first rib or transverse processes of vertebrae and heads of ribs. In most other cases a prominent linear margin, seen in films of excised lungs, is covered by the curvatures of the ribs forming the lateral boundary of the lung field. Only when the pleura is more than 2 mm. thick and covers a fairly extensive area will it cause, on a chest film, a mottling of light density indistinguishable (except perhaps by stereoscopy) from conditions within the lung substance. It is reasonable to anticipate that such a prominent lateral border could occasionally be brought out in an induced partial pneumothorax.

In 7 instances the pleura showed thickening in regions other than the apices ; this was revealed in the excised lung film in 4, and in the chest film in 1, instance. Obliteration of the interlobar fissures was met with in 7 bodies, was recognized as a linear opacity in the excised films in 6 of these, and in the chest films in 3. Although at autopsy fibrous obliteration affected all the fissures equally, such obliteration was only recognized in the chest films in the case of the fissure between the right upper and middle lobes. This always appeared as a horizontal linear opacity, and is due to the fact that the plane of this fissure lies parallel to the rays. The other fissures are more oblique, but if obliterated by dense fibrosis may show in good antero-posterior exposures as mottling of the lung fields indistinguishable from other intra-pulmonary lesions. Adhesions of the pulmonary bases to the diaphragm produced no changes recognizable in our films; peaking of the diaphragm and obliteration of the costophrenic and cardiophrenic angles would be obscured by the high position of the diaphragm found in the cadaver lying in a horizontal position.

Peripheral Focal Lesions.

These consisted of isolated and discrete pathological foci scattered irregularly throughout the lungs, but with a special affinity for the peripheral and subpleural zones. These lesions are generally of small size and consist of calcified, caseous, or fibrous foci—often a combination of two or more of these. They were found in 26 instances (72 per cent. of cases). This figure, rather low when compared with that given by Opie (14), may be partly explained by the high incidence of gross pathological changes encountered in this series, making the identification of these lesions very difficult. Their occurrence was slightly more frequent in coloured (73·3 per cent.) than in white (71·4 per cent.) subjects, and in males (75 per cent.) than in females (68·7 per cent.). They were found in all lobes, but were more frequent and conspicuous in the lower lobes, and slightly more on the right side than on the left. The significance of these changes will be discussed later.

The large majority of these focal lesions were completely calcified. With the help of the radiograms of excised lungs, a greater number could be identified by dissection than without such help. Of nine cases where their size was less than 2 mm. in diameter, four were seen in the chest plates, and these generally

in the mid zone of the lung field and in areas free from bony structures; they were readily obscured by pulmonary congestion or oedema. In eleven cases the lesions were from 3 to 5 mm., and these were recognized in chest plates in seven instances. In four cases lesions from 0·5 to 1 cm. diameter were present, were readily detected in two plates, and could be seen through ribs or clavicles. In one case where a node was greater than 1 cm. diameter it could be readily seen in the films (Pl. 25, Fig. 9). Case 29 (Pl. 26, Fig. 10) shows a node just above the left diaphragm, which was actually present in the base of the left upper lobe (see Table II).

Caseous lesions varying from 0·5 to 1·5 cm. diameter and usually of firm consistency were found in six autopsies (one showing necrosis with cavity formation). All were accurately outlined in the films of excised lungs and five were seen in the chest plates. They were all of old standing and, as already stated, were probably infiltrated with calcium, although this was not recognized macroscopically.

Fibrous nodules, deeply pigmented, were found in eight autopsies varying from 0·5 to 3 cm. diameter. They were recognized in four instances in films of excised lungs. These were seen in the chest plates on three occasions; from their density in the films of the excised lungs it was obvious that they were of old standing and infiltrated with calcium. At the autopsy a narrow zone of fibrosis surrounding calcareous and caseous foci was frequently found, but could not be differentiated from normal lung tissue in either of the radiograms.

Apical Lesions.

Pathological changes occurring within the lung parenchyma in the upper 4 cm. of the upper lobes were detected in sixteen autopsies. They are summarized in Table III and include changes varying from slight fibrosis to obvious calcification, caseation, and cavitation. Whilst all are presumed to be of tuberculous origin, the evidence was only considered as certain where either caseation, calcification, or cavitation existed. The lesions were bilateral in seven, on the right side only in five, and on the left only in four cases; seven occurring in men and nine in women. As will be shown, several smaller lesions would have been overlooked but for the radiogram of the excised lung. In the case of slight fibrosis (i.e. an area involving less than 0·5 cm. diameter) there was evidence of it in the chest plate in one of the two cases. In eleven instances of moderately dense fibrosis occupying areas up to 3 cm. diameter, only five were recognized in the chest plates. In the majority of those not seen the lesion occupied either the extreme tip or the inner aspect of the apex, and was thus covered by the structures elsewhere described. Calcified nodules were recognized in the chest plates in a third of the cases (Pl. 25, Fig. 10). Firm caseous foci of old standing were recognized in both instances in which they were found *post mortem*. In four instances of cavitation two were recognized in the chest plates. It is interesting to note that the degree of visibility does not depend on size, for the largest cavity, measuring 6 cm. in its greatest diameter, was not seen, whereas the smallest, measuring 2 cm. across in its greatest diameter, was visible in the chest plate.

Some of the factors upon which the visibility of cavities depends have already been discussed.

Tuberculosis of Tracheobronchial Lymph Nodes.

No attempt to tabulate the cases investigated has been made, since the problem of their recognition has been fully discussed by McPhedran (6), and the small number of cases here considered confirms his conclusions. It is interesting to point out that shadows due to calcareous infiltration were frequently seen in the films of excised lungs, especially in the intra-pulmonary nodes, that could not be seen macroscopically on most careful dissection. With the exception of very massive nodes (e. g. Case No. 34) simple fibrosis or inflammatory hyperplasia could not be seen in any radiograms. It was noteworthy that even in very gross tuberculosis of tracheobronchial lymph nodes, the process was invariably limited by the gland capsule and in no case invaded the surrounding connective tissue. For this reason the term 'Hilum Tuberculosis' is apt to be misleading and fails to give an accurate conception of the pathology of this condition. It is important to note that manifest disease of parabronchial lymph nodes may be recognized in the lung substance and frequently produces densities in the plates for at least one-third of the way to the periphery of the lung field. It is in regions peripheral to the hilum that even small areas of caseation or calcification may be most easily recognized in films. Macroscopic change suggesting a tuberculous origin was found in 25 instances. In 20 of these cases, focal lesions were present in the lung tissue, and generally in the zone drained by the affected nodes (Pl. 25, Fig. 9 and Pl. 26, Fig. 10). Much significance cannot be attached to the five cases where pulmonary focal lesions could not be identified, since some of them were undoubtedly overlooked in this series. The pathological change in the lymph node was always of greater extent than in the associated lung tissue. A corresponding relationship between apical lesions and those of tracheobronchial nodes was not observed.

Of other lesions encountered, infarcts, though well seen in films of excised lungs, were not seen in any of our chest plates. They were generally at the pulmonary bases and hidden by the diaphragm. Secondary sarcomatous deposits produced opacities in chest radiograms, having approximately the same density as pneumonic infiltrations of corresponding extent. The prominence of hilum and trunk shadows in chest plates has already been discussed.

We have thus seen that the lesions most frequently recognized in radiograms are the focal calcified or caseous nodes. Of apical lesions, the majority of the smaller ones, occurring as they do either at the extreme tip or on its inner aspect, were not detected in the chest radiograms in this study.

Discussion.

The study of latent or non-progressive tuberculosis in adults reveals two varieties of lesions, each having distinctive characters well recognized by many workers.

The primary lesions due to the first infection are found as the focal scattered lesions in all the lobes; they are unusually small, frequently calcified, and found in a high percentage of adults living in civilized communities. The consistency and nature of these nodules are evidence of considerable age, and Küss (5), Ghon (1), and more recently Opie (14), have shown that they are typical of the lesions sustained during childhood. The fact that their presence indicates a relatively mild infection overcome by the patient is of great importance. Tuberculous infection under 2 years of age is fatal in a large number of cases, but after this there is an increasing tendency for healing to occur with the formation of caseous and calcareous nodes. Though not concerned here with the mode of infection, it may be noted that much of the evidence in the literature suggests an aerogenous route. Parrot (19) stated in 1876 that a lesion in the tracheobronchial lymph nodes was always associated with a lesion in the region of the lung drained by them, and that the converse was equally true. This has always been the subject of much controversy, though strongly supported by such subsequent workers as Küss (5), Ghon (1), and Opie (16). In this investigation it has been shown that there have been few exceptions to this rule. Although the changes in the lymph nodes have invariably been more extensive than those in the lung tissue, the close relationship has generally been easy to demonstrate. With lesions of the inner segment of a lower lobe, the lymph nodes in the *ligamentum pulmonale* were occasionally involved, whereas in all other areas the corresponding intra- or extra-, frequently both, pulmonary tracheobronchial nodes were affected. In view of the great difficulty met with in tracing many of the minute lesions, the obscuring effects of gross pathological change not infrequently encountered, and the absence of routine microscopic examination of lymph nodes, too much significance cannot be attached to the few instances in which a strict correlation between the pulmonary and lymph-node changes could not be demonstrated.

The nature of the pulmonary focal nodules was generally consistent with the view that they were of older age than the disease processes in the corresponding lymph nodes. The recent work of Miller (8) on the pulmonary lymph flow makes it difficult to accept the view that a retrograde infection from the hilum to the lung tissue can occur. Krause (4) has shown experimentally that organisms may pass through the lung tissue, leaving the latter unaffected, and produce the primary lesion in the lymph nodes. If this occurs in man it must do so infrequently. The demonstration of the older and smaller foci in the lung is greatly facilitated by the use of X-ray apparatus in the autopsy room, and this study does not lend support to the view held by many authors that primary tracheobronchial tuberculosis is of frequent occurrence.

The second variety of lesion is that occurring at the apices of adults. This is characterized by fibrosis rather than by calcification, and shows considerable tendency to ulcerate. It appears in adolescence or adult life and seldom before 11 years of age. Opie (14) has shown that apical tuberculosis of adults appears after the primary or childhood tuberculous foci to which it is in no way related anatomically. Frequently it is seen on the opposite side to that of the focal or

primary lesions and is unlike them in that the neighbouring lymph nodes are not involved. Further, it has been shown that such apical disease appears when tubercle bacilli have already disappeared from the primary foci (17). Thus, as was pointed out by Opie (14 and 16), the apical lesions of adults do not result from the same infection that produces the primary focal nodules, but have all the characters of a second or re-infection taking place in an individual who has already overcome a previous infection. This is comparable to an experimental re-infection in animals, which, as demonstrated by Koch (3) produces a lesion differing from that of the first infection in that localization and healing occur without involvement of the corresponding lymph nodes. The primary foci need not necessarily occur in the lungs; they may be encountered in the abdomen and manifested in the mesenteric nodes. In Case 37, where large and completely calcified mesenteric nodes were present, only a few sparsely scattered focal lesions measuring up to 1 mm. diameter could be found in the lungs.

Where in an adult, first infection takes place on virgin soil, it is apt to progress in a rapid manner, produce focal lesions showing acute caseation and pneumonic infiltration, and be associated with gross involvement of the tracheobronchial lymph nodes. It has been shown (Opie (15)) that adult negroes are especially liable to this type of 'infantile' tuberculosis, and that acute miliary tuberculosis is at least $4\frac{1}{2}$ times more frequent amongst them than amongst the white races. In Case 34 of this series, a male negro aged 49, this type of infection is well illustrated (Pl. 21, Fig. 5). The primary lesions were at the apex of each lung and appeared as recent, soft, caseous foci showing no tendency either to fibrosis or localization. It is noteworthy that no healed calcified or fibrous focal lesions could be detected, and this would explain the poor resistance and the rapid progress of the disease. In two autopsies on white adults (Cases 10 and 19) where death was due to an acute and rapidly progressive pulmonary tuberculosis, healed primary foci could not be found. In the third (Case 18) where the pathological process was of a slower and older kind, healed calcified nodules were readily demonstrated.

The recognition of early or latent disease is of the greatest importance to both the individual and the community. For if early disease manifesting itself by physical signs can so often be arrested, the detection of lesions before manifest symptoms occur, will frequently enable the individual to live under conditions in which active disease can be prevented.

The presence of such early lesions have a further significance in that they always indicate exposure to infection, the source of which is usually 'open' tuberculosis—i.e. patients coughing up living tubercle bacilli, within the family. A study of tuberculosis in families by Opie and McPhedran (18) has shown that latent focal pulmonary tuberculosis associated with tracheobronchial disease is at least seven times more numerous in contact than in non-contact families. Moreover, the size and frequency of the lesions have a direct relationship to the length of exposure.

It has been shown that although tubercle bacilli have generally disappeared

from the circumscribed peripheral foci by the time apical tuberculosis appears, these apical latent lesions contain viable bacilli in a high percentage of cases (Opie and Aronson (17)). Whereas the calcified focal lesions have only a limited clinical significance in adults, the apical lesions may be the source of more widespread pulmonary or even generalized tuberculosis (11). Furthermore, individuals having such lesions, though without symptoms at the time, may not only be a menace to themselves, but may unsuspectingly be a source of infection to others.

Summary and Conclusions.

1. An attempt has been made to correlate the anatomical features of healed and latent tuberculous lesions of the lungs with the radioscopic appearances of the thorax. The limited number of cases investigated does not justify the formation of definite conclusions of a general nature.

2. The method used has been described and its advantages and limitations indicated.

3. Radiograms of the aerated excised lungs revealed abnormal shadows as the result of most macroscopic pleural and pulmonary lesions seen at autopsy. Calcified lesions of 1 to 2 mm. diameter, and fibrous changes greater than 0·5 cm. in extent can usually be recognized provided they are not obscured by more widespread disease such as oedema or congestion.

4. Radiograms taken of the cadaver lying in a horizontal position seldom show as much detail as those taken in the erect posture during life. Those taken for the purpose of this investigation have shown:

(*a*) That the majority of pleural lesions, occurring as they do at the apices of the upper lobes were not recognized. Changes limited to the pleura over the diaphragmatic surfaces of the lower lobes did not produce visible abnormalities. Only when extensive, did thickening of the pleura covering the costal surfaces of the lungs produce a diffuse mottling indistinguishable (in the absence of stereoradiograms) from that produced by intra-pulmonary disease.

(*b*) That fibrous obliteration of the interlobar fissure between the right upper and middle lobes was sometimes recognized as a horizontal linear opacity. Similar obliteration of the other fissures produced a diffuse mottling of the lung field.

(*c*) That a large number of small lesions in the upper 2 cm. of the upper lobes were not seen. Of the cases showing intra-pulmonary apical lesions at autopsy, less than half were recognized radioscopically. Changes in the inner thirds of the supraclavicular regions, the inner fifths of each lung, the region overlapped by the heart, and the right base, were generally obscured.

(*d*) That calcified peripheral focal lesions occurring in uncovered zones, and when not obscured by gross pulmonary disease, produced recognizable opacities between the rib-shadows, when 2 mm. or even less in diameter. When 5 mm. or more in diameter, the resulting opacities could be seen through the ribs.

(*e*) That fibrous lesions, except when very dense in structure, were seldom recognized unless over 1 cm. diameter.

(*f*) The difficulty of judging the size of a cavity by radioscopic appearances, and the possibility of simulation by other pathological changes.

5. The significance of the peripheral focal tuberculous lesions, their relation to apical tuberculosis of adults, and the relation of both the peripheral and apical lesions to tuberculosis of the tracheobronchial lymph nodes were discussed.

6. The radioscopic appearances produced by some commonly encountered non-tuberculous pulmonary lesions were described.

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TABLE I. *Pleural Lesions.*

	Number showing lesions limited to apex.	Number showing lesions of apex and other parts of lung.	Lesions of pleura in areas other than apex.	Number with obliteration of interlobar fissures.	Total cases showing lesions.	Total cases examined.
At autopsy	17	9	7	7	32	36
In radiograms of excised lungs	16	8	4	6	21	36
In radiograms of chest	2	3	1	3*	6	36

* These showed only in the fissure between right upper and middle lobes.

TABLE II. *Peripheral Focal Lesions.*

	Number of cases showing calcified lesions.					Showing caseous lesions.	Showing fibrous lesions.	Total number of cases showing focal lesions.	Total cases examined.
	Under 2 mm.	From 3–5 mm.	From 0·5 to 1 cm.	Over 1 cm.	Of any size.				
Seen at autopsy	9	11	4	1	20	6*	8*	26	36
Seen in radiograms of excised lung	10	12	3	1	18	6	4	—	36
Seen in radiograms of thorax	4	7	2	1	12	5	3	—	36

* As determined macroscopically: calcium infiltration was not excluded by microscopic examination.

TABLE III. *Apical Lesions.*

	Slight fibrosis.	Moderately dense fibrosis.	Calcification under 2 mm. diameter.	Calcification over 3 mm. diameter.	Caseation	Cavitation.	Total cases showing lesions.	Total cases examined.
Seen at autopsy	2	11	3	3	2	4	17	36
Seen in radiograms of excised lungs	2	10	4	3	2	4	14	36
Seen in radiograms of thorax	1	5	1	1	2	2	7	36

Description of Lesions with Explanations of Plates 18 to 26.

Fig. 1. Radiogram of Excised Lungs.

Case 23. A. Y., white female, aged 70. Sudden onset of hemiplegia; died in coma. No history of pulmonary disease.

Autopsy. Generalized arterio-sclerosis. Cerebral atheroma. Cerebral haemorrhage.

Lungs. Right. The pleura over the upper lobe was greatly thickened, extensively adherent to the chest wall, and scarred and puckered over the apex. The lung tissue at the apex was airless and fibrotic, and continuous with the thickened pleura were two densely sclerotic areas, each measuring $7 \times 5 \times 5$ mm. At the lower and outer quadrant was an area of fibrosis, measuring $5 \times 5 \times 4$ cm., the cut surface of which showed dilated bronchi containing pus. Along the anterior free margin were three deeply pigmented fibrous nodules, having gritty calcareous centres; the largest of these measured $1 \times 0{\cdot}7 \times 0{\cdot}7$ cm.

The middle and lower lobes were congested, and in the latter consolidated areas of broncho-pneumonia were present. Two subpleural nodules of cartilaginous consistency, each 2 mm. diameter, were detected on the inner aspects of the lower lobe.

Left. The apical pleura over the upper lobe was thickened in two areas; one, at the extreme apex, measured $1{\cdot}5 \times 1$ cm., was 2 mm. thick, densely fibrotic, and moderately calcified. On the outer aspect of this lobe were two subpleural calcified nodules, each 1 mm. diameter and surrounded by a narrow zone of pigmented fibrous tissue. At its lower and outer part was a shrunken wedge-shaped zone of fibrosis with dilated bronchi filled with pus.

The lower lobe was moderately congested.

The cartilages of the trachea and bronchi down to those of the 4th degree were calcified. There was no evidence of thickening of the walls by peribronchial fibrosis.

Below and to the right of the bifurcation of the trachea was a mass measuring $4{\cdot}5 \times 3 \times 2$ cm. consisting of several fibrotic and partially calcified adherent tracheobronchial lymph nodes. Above the right bronchus was an extra-pulmonary node, $2{\cdot}5 \times 1{\cdot}5 \times 1$ cm., having a calcified centre. Many other smaller fibrotic and often calcified parabronchial nodes were seen both outside and within the lung, particularly in the right lower lobe.

Radiogram of excised lungs. The right lung is incompletely distended. The outer margins, particularly of the upper and lower lobes, are irregularly opaque from thickening of the pleura. At the apex are two moderately dense opacities, the outer and larger being roughly triangular and extending in from the surface. At the lower fourth of this lobe is a roughly triangular shadow of mottled density.

The right middle lobe is relatively better distended and partially overlaps the upper lobe. The lower fourth of this is occupied by a triangular mottled shadow, due partly to congestion, and almost as dense as that in the right lower lobe produced by fibrosis. Within this area is a well-defined, dense oval opacity, and above this zone is a much larger but irregular opacity of moderate density. The first corresponded to a completely calcified subpleural nodule, and the second to a larger fibrotic nodule only partially impregnated with calcium.

The right lower lobe is occupied by a large triangular zone of mottling, the lighter part corresponding to congested areas, and the denser to consolidated broncho-pneumonic areas.

At the apex of the left upper lobe is a small irregular shadow, part of which is sharply defined and densely opaque. This is almost entirely pleural in origin, though appearing within the lung field. At the outer and lower angle of this

lobe is a homogeneous shadow, extending inwards and upwards towards the hilum, from an irregular and puckered margin. This was the result of fibrosis.

The larger bronchi produce very prominent markings, mainly because of calcification of their cartilages. In the neighbourhood of the larger bronchi are a number of roughly circular shadows produced by diseased tracheobronchial lymph nodes; the larger and lighter result from fibrotic, and the smaller and denser from calcified nodes.

Scattered throughout the lung field are small densities, many not greater than 1 mm. in diameter. Some of the more conspicuous of these have already been noted. For the most part they correspond to subpleural calcified foci found at autopsy.

Radiogram of thorax (cadaver). The trunk markings are unduly prominent and beaded, and distinctly seen as far out as the junction of the outer with the inner three-fourths of the lung field.

Some irregular and ill-defined shadows are seen to the right of the hilum, and one small well-defined opacity, produced by a calcified lymph node was seen beneath the sixth rib, 7 cm. to the right of the mid line.

The lower half of the right lung field was irregularly mottled. The apices were clear; the opacities seen in the radiograms of the excised lungs due to pleural changes were covered by the first rib.

Fig. 2. Radiograms of Excised Lungs.

Case 12. E. M., coloured male, aged 36. Admitted to hospital for aortic incompetence, and died of cardiac insufficiency.

Autopsy. Great hypertrophy and dilatation of the heart, aortic incompetence, and extensive syphilitic mesaortitis.

Lungs. Both lungs showed moderately advanced, recent passive congestion, particularly at the bases.

At the base of the right lower lobe was a roughly wedge-shaped, firm infarct, showing evidence of commencing organization, and measuring $7 \times 3 \times 3$ cm. The pleura over its base was adherent to the diaphragm. Throughout both lungs were a few sparsely scattered calcified nodules, most of which were about 1 mm. diameter.

The tracheobronchial lymph nodes at the right hilum were enlarged up to $5 \times 3 \times 2$ cm., soft, fleshy, and pigmented, but neither fibrotic nor calcified. A few partially calcified intra-pulmonary nodes were noted on the left side.

Radiogram of excised lungs. Both lung fields show diffuse mottling, more marked on the left than on the right, the variations corresponding with the degree of congestion found at autopsy.

At the right base is a well-defined homogeneous shadow produced by the infarct, of similar density to that resulting from the zones of more advanced congestion.

Some minute focal shadows are seen here and there; more conspicuous ones are present in both lower lobes.

The calcified parts of the intra-pulmonary tracheobronchial nodes on the left side are recognized as small densities near the bifurcation of the left bronchus, but the much larger non-calcified nodes on the right side cast no shadows whatever.

Radiogram of thorax (cadaver). There is a considerable amount of stippling at the left base and in the right mid zone. The shadow produced by the infarct, overlapped by that of the liver, does not appear in this radiogram. The hilum lymph nodes are not recognizable.

Fig. 3. (*a*) *Radiogram of Excised Lungs.* (*b*) *Radiogram of Thorax.*

Case 13. M. P., white female, aged 50, admitted with hemiplegia and heart failure. Died of cardiac insufficiency.

Autopsy. Syphilitic mesaortitis. Dilatation of heart; organized infarct of anterior wall of left ventricle, having a large ante-mortem thrombus attached to its inner wall.

Lungs. Right. The upper and middle lobes were extensively adherent to the chest wall by fibrous adhesions. The pleura was puckered over the apex of the upper lobe and thickened over the antero-lateral and posterior aspects of the upper and middle lobes. The subjacent lung tissue showed no obvious abnormality.

The lower lobe showed moderate passive congestion, and at its posterior and inferior aspects was a recent haemorrhagic infarct measuring $5 \times 3 \times 3$ cm.

Both inter-lobar fissures were obliterated by fibrous adhesions.

Left. The apical pleura of the upper lobe was puckered and thickened. On its inner aspect, 10 cm. below the apex, was a small subserous calcified nodule, $3 \times 3 \times 1$ mm.; the remainder of this lobe was free from gross pathological change.

A few centimetres below the apex of the lower lobe were two small subserous calcified nodes, one on the anterior and the other on the posterior aspects. At the anterior and inferior angle of this lobe the pleura was thickened, impregnated with calcium, and adherent to the diaphragm over an area of 1 square cm. There was some passive congestion throughout the mesial half of the lower lobe.

The tracheobronchial nodes along the right bronchus were enlarged and measured up to $3{\cdot}5 \times 2 \times 2$ cm. The larger of these were partially caseated and calcified.

Radiogram of excised lungs. The fields of the right upper and middle lobes are irregularly mottled. This can be accounted for by little else than extensive pleural thickening. From the same cause the margin over part of the upper lobe is heavily outlined.

In the right lower lobe a similar, but denser mottling is present, and the trunk markings are unduly prominent. Here passive congestion was the only obvious abnormality, except at the base, where an infarct is represented by a roughly rectangular homogeneous shadow.

The left lung field is moderately clear and represented by normal anatomical architecture. The margin over the tip of the upper lobe is seen as a thin linear opacity, and at the lower and outer angle of the left lower lobe is a small, well-defined density. Both are due to pleural changes. The inner half of this lobe is occupied by a diffuse mottling of light density.

Small scattered focal opacities are seen throughout both sides, but more clearly on the left. Those lying away from trunk markings are caused by peripherally situated calcareous or densely fibrotic lesions, and, with the exception of two along the inner margin and lying a few centimetres below the bifurcation of the left main bronchus, were less than 1 to 2 mm. in diameter. Similar opacities are seen along the trunk markings and at the angles where they divide, and result from the rays striking the branches of vessels or bronchi in their long axis: such opacities are not constant when specimens are X-rayed in more than one plane.

Two large and roughly oval, ill-defined opacities above and below the right main bronchus correspond to enlarged lymph nodes containing calcium.

Radiogram of thorax (cadaver). The left supraclavicular area is clear; the right is occupied by a light density beneath the third rib.

The lung structure of the right side is partially obscured by a diffusely mottled shadow extending from the clavicle to the base. Commencing externally at the level of the fourth rib on the right side, a well-defined horizontal linear

opacity, corresponding to the fissure between the upper and middle lobes, extends in towards the hilum.

Shadows produced by peripheral focal lesions, and the infarct at the right base, are not seen.

Fig. 4. (*a*) *Radiogram of Excised Lungs.* (*b*) *Radiogram of Thorax.*

Case 19. R. M., coloured male, aged 21, admitted to hospital in stuporose state with signs suggestive of meningitis; history unobtainable. Died shortly after admission.

Autopsy. Pulmonary tuberculosis. Caseating tuberculosis of suprarenals. Tuberculous meningitis.

Lungs. Left. The pleura covering this lung was adherent to the chest wall and mediastinum by thin fibrous adhesions. The interlobar fissure was obliterated.

Near the apex of the upper lobe was a roughly oval cavity, $5 \times 3 \times 2$ cm., containing caseating and partly purulent debris. The tissue round the cavity was irregularly consolidated over an extensive area and studded with numerous grey, miliary, granulomatous tubercles up to 2 mm. diameter. Throughout the lower and inner quadrant of this lobe there was confluent tuberculous broncho-pneumonia: this area was also studded with numerous, discrete, granulomatous tubercles. At its base was a small cavity, $3 \times 2 \times 1{\cdot}5$ cm., produced by the breaking down of an area of confluent caseating broncho-pneumonia.

Section of the lower lobe, particularly in its inner half, showed numerous discrete broncho-pneumonic nodules up to 6 mm. diameter.

Right. The pleura covering the costal and diaphragmatic surfaces was fibrous, in places up to 5 mm. thick, and adherent to adjacent structures on all its aspects. Both interlobar fissures were obliterated by dense fibrosis.

At the apex of the upper lobe, extending downwards from its tip, was an oval loculated cavity, $3{\cdot}5 \times 1{\cdot}5 \times 1{\cdot}5$ cm., surrounded by a broad zone of dense fibrosis. The cut surface of the upper part of this lobe was beset with numerous grey, miliary, granulomatous tubercles up to 3 mm. diameter. The lower third of the right upper and the greater part of the right middle and lower lobes were consolidated, and on section showed numerous confluent tuberculous broncho-pneumonic areas, with occasional isolated, small, miliary tubercles.

The tracheobronchial nodes on both sides were enlarged and discrete. On the left side some were completely, and others partially, calcified.

Radiogram of excised lungs. Left. The outer margin of the left upper lobe is seen as a thin linear opacity. The fissure between the upper and lower lobes is represented by a thin but relatively dense line.

The inner and upper half of the upper lobe is occupied by a densely mottled opacity, gradually fading off as the periphery is approached. In the upper part of this opacity is a well-defined bilocular area of lighter density, 5×3 cm. At the base of this lobe is an irregular shadow of considerable density, having within it a sharply defined oval lighter area, $1 \times 0{\cdot}5$ cm.

At the upper two-thirds of the lower lobe is an extensive opacity, very dense near the hilum, but gradually becoming less so and more heterogeneous as the periphery of the field is approached.

Right. The outer margin of the upper and middle lobes and the inner margin of the lower lobe are heavily and thickly outlined. Both interlobar fissures are similarly defined as thick dense lines.

The lung fields of all three lobes are obscured by very opaque diffuse densities, becoming lighter as the periphery is approached. (Part, at least, of this opacity is due to the thickened pleura seen at autopsy).

In the centre of the homogeneous opacity filling the upper lobe is a circular area of lighter density, about 1 cm. diameter, and at the lower and outer angle of

this lobe is a similar but larger area. The upper of these corresponds in position with a cavity found at autopsy about three times larger than the area in the film; corresponding to the lower area was a small zone of emphysematous lung, but no cavity.

Radiogram of thorax (cadaver). The left lung field is occupied by an extensive, patchy, and irregular mottling increasing in density at the hilum. Between the second and fourth ribs is an elongated oval and well-circumscribed light area, 4 × 3 cm.

Throughout the right side is a more uniform and homogeneous opacity, becoming lighter towards the costophrenic angle. This side of the thorax is roughly bisected by a horizontal linear density at the level of the fourth rib. Nothing suggestive of cavity can be recognized in the region of the right apex.

Fig. 5. (*a*) *Radiogram of Excised Lungs.* (*b*) *Radiogram of Thorax.* (*c*) *Photograph of Specimen.*

Case 34. I. L., coloured male, aged 49, admitted to hospital with unexplained pyrexia. The spleen and liver were enlarged. Examination of lungs revealed coarse bubbling crepitations on auscultation of bases. No previous history of tuberculosis.

Autopsy. Acute disseminated, miliary tuberculosis, with pulmonary lesions of the 'Infantile' type. Spleen enlarged and studded with discrete caseating nodules. Miliary and submiliary, granulomatous tubercles throughout the liver, cortex of kidneys, and suprarenals. Brain not examined.

Lungs. Both were extensively adherent to the thorax and diaphragm by thin fibrous adhesions. They were bulky, heavy, and firm.

The cut surfaces of all lobes had a moist, grey, and gelatinous appearance, and were thickly studded with numerous discrete, and at times conglomerating, granulomatous tubercles of all sizes up to 1·5 × 1 × 1 cm. These were more numerous towards the periphery of the lungs and for the most part irregularly arranged, though occasionally, as in the right lower lobe, they were radially distributed in a fan-shaped manner extending outwards from the hilum.

At the apex of the left upper lobe, just beneath the pleura, was a small irregular area of caseation measuring 2·5 × 2 × 1·5 cm. and undergoing necrosis and liquefaction. At the apex of the right lower lobe extending downwards from its tip was a yellowish-grey area of firm caseating material similar in size to that in the left apex.

At the hilum was a well-defined encapsulated, entirely extra-pulmonary lobular mass, roughly the size of a large orange, and consisting of discrete and adherent lymph nodes, the largest measuring 7 × 5 × 4 cm. The greater part of this lay in front of the trachea and main bronchi, but partly surrounded them, as well as the aortic arch and its branches. With the exception of two smaller nodes below, showing small areas of caseation and necrosis, the greater part of the mass was tough, firm, and fibrous. Microscopic sections showed that the greater part of this mass consisted of dense pigmented fibrosis with rare areas containing giant cell systems undergoing necrosis. No evidence of calcification was seen.

Calcified focal lesions could not be detected in any parts of the lungs, nor could healed tuberculous lesions be found in any part of the body.

Radiogram of excised lungs. The normal markings of both lungs are obliterated by a diffuse heterogeneous mottling which does not increase towards the hilum (compare cases of broncho-pneumonia).

Near the apex of the left upper lobe is an annular shadow enclosing a lighter area. The fissure between the right middle and right lower lobes is represented by a thin linear opacity.

Crossing from the upper part of one lung to the other is a well-defined saddle-shaped homogeneous shadow. This corresponds to part of the lymph-adenoid mass at the hilum, which was extra-pulmonary, and which was neither

caseous nor calcified. On the right side and below the main shadow is a smaller, oval, and less sharply defined shadow.

Focal densities are not seen in any part of the pulmonary field suggestive of calcified lesions.

Radiogram of thorax (cadaver). There is a diffuse and more or less evenly distributed mottling throughout both lung fields. This is produced by very numerous ill-defined shadows of varying density and generally less than 1 cm. diameter.

Opposite the fourth to the seventh ribs, a shadow of homogeneous density, and with well-defined lateral margins, extends outwards from either side of the hilum, more to the right than to the left.

Fig. 6. Radiogram of Excised Lungs.

Case 3. A. K., white male, aged 55, died of chronic nephritis. No past history of chest disease.

Autopsy. 'Chronic interstitial nephritis': cardiovascular hypertrophy.

Lungs. The left upper and lower lobes were adherent to the chest wall over their outer aspects by fibrous bands. The pleura over the apex of the left upper lobe was thickened and puckered. Within the subjacent lung tissue, and 1 cm. below the tip, was a dense fibrotic nodule, 4 × 4 × 4 mm.

Extending from the posterior surface of the apex of the right upper lobe was a small patch of fibrosis within which a small calcareous nodule, 2 mm. diameter, was embedded. About 4 cm. below this and 1 cm. deep to the outer surface, was an irregular fibrotic nodule about 0·5 cm. diameter.

Several minute, subserous, fibrous, and partially calcified foci were found throughout both lungs, and on the inner aspect of the right lower lobe was a somewhat larger and completely calcified one.

Both lower lobes were congested and oedematous.

The hilum lymph nodes showed no obvious pathological changes.

Radiogram of excised lungs. The apex of each upper lobe is capped by an irregular opacity extending into the lung field from the margin. At the inner end of the opacity at the left apex is a small area of great density, and beneath the outer part of that on the right side is a similar but smaller one.

There is considerable mottling throughout both lung fields, more marked in the lower portions.

Several small circular opacities from 1 to 2 mm. diameter are seen on both sides, and beneath the inner margin of the right lower lobe is one more sharply defined than the rest.

The irregular shadows above the bifurcation of the trachea are due to calcareous plaques in a part of the aorta which was not completely removed.

Radiogram of thorax (cadaver). There was considerable mottling at both bases. No abnormal shadows could be detected at the apices.

This represents a type of case not infrequently seen: the presence of healed or latent lesions at the extreme apices that cannot be detected in the radiograms of the thorax by ordinary technique.

Fig 7. Radiogram of Excised Lungs.

Case 8. M. K., white female, aged 54. Died of acute intestinal obstruction. No previous history of phthisis.

Autopsy. Carcinoma of left ovary; secondaries of peritoneum; intestinal obstruction and general peritonitis.

Lungs. Right. The visceral pleura over the outer aspect of the upper lobe was thickened and adherent to the parietal layer. At the apex of this lobe it was puckered, and on section was continuous with a wedge-shaped area of

fibrosis, 3 × 2 × 2 cm., the peripheral part of which was dense and slightly gritty on section.

The lower lobe showed moderate congestion. Several subpleural fibrous and calcified nodules were detected on more careful dissection: one measuring 5 × 3 × 2 mm. and calcified was found at the upper part of this lobe 2 cm. below the outer surface.

Left. The pleura over the summit and outer aspect of the upper half of the upper lobe was thickened, puckered, and adherent to the chest wall. Extending in from the summit of this lobe the lung parenchyma was replaced by a wedge-shaped area of loose fibrous tissue.

Both in the upper and lower lobes a number of calcified nodules were detected, usually near the periphery. The largest of these, found a few centimetres below the apex of the upper lobe, measured 3 × 3 × 2 cm. Some congestion and oedema were present in parts of both lobes. At the right hilum was a stony hard, intra-pulmonary crenated lymph node, 2·5 × 1 × 1 cm., and a little deeper was a smaller calcified parabronchial lymph node.

Radiogram of excised lungs. There is extensive mottling in both lung fields. A number of small, oval or circular shadows of considerable density are seen in all lobes; in the left upper and right lower are some of larger dimensions.

The outlines of the upper borders of both upper lobes are irregular, and at the right apex is a shadow of marked but varying density.

Shadows due to calcified lymph nodes are seen near the right hilum beneath the marking of the right bronchus.

Radiogram of thorax (cadaver). Both lung fields are mottled—the right more than the left. With the exception of the dense shadow at the right apex, most of the larger opacities seen in the radiogram of the excised lungs may be recognized in the film of the thorax. At the left upper lobe there are two small densities corresponding to those seen in the film of the excised lungs; the inner is seen through the inner aspect of the second rib, and the outer just below the clavicle.

The density in the right lower lobe is recognized through the outer end of the seventh rib, and that due to the larger calcareous lymph node is just seen through the right half of the cardiac shadow.

Fig. 8. Radiogram of Excised Lungs.

Case 30. S.W., white female, aged 53 years. Admitted to hospital with a large mass in abdomen, evidence of pericardial effusion, and indefinite signs in the lungs. Died soon after admission.

Autopsy. Large sarcomatous mass replacing substance of the right kidney and filling right half of abdomen. Secondary deposits of growth on pericardium invading the myocardium; blood-stained pericardial effusion.

The right pleural cavity contained 8 ounces of dark blood-stained fluid.

Lungs. Throughout both lungs were well-defined spherical nodules of reddish-grey, vascular growth. The pleura was occasionally bulged by these nodules which showed a tendency to a peripheral distribution. On the right side both visceral and parietal layers were invaded by two such nodules. In the case of the larger nodules, which occasionally fused with each other and measured up to 6 × 5 × 5 cm., necrosis occurred in their centres, and in some instances, as in the left lower lobe, were cystic and contained a thin, clear, brownish fluid.

At the apex of the left upper lobe the pleura over the inner aspect was thickened and of cartilaginous consistency over an extent of 3 square cm. This was continuous with an ill-defined block of fibrosis extending into the subjacent lung tissue measuring 2 × 2 × 1 cm. On the antero-inferior angle of the right lower lobe the pleura was greatly thickened and continuous with a small patch of densely fibrotic tissue measuring 1 × 0·5 × 0·5 cm.

Scattered throughout both lungs were minute fibrous nodules of cartilaginous

consistency up to 3 mm. in diameter, some attached to the pleura and others somewhat more deeply situated. In rare instances these were calcareous.

The tracheobronchial lymph nodes were enlarged, soft, and pigmented, measuring up to 3·5 × 3 × 2 cm. on the right side. There was no obvious infiltration with growth or calcium.

Radiogram of excised lungs (slightly over-inflated). Circular shadows of great density are noted on both sides. These are generally sharply defined and in obvious contrast with the remaining lung field, which, for the most part, is normal in appearance. These opacities are more frequent at the periphery of the lobes, and at times occupy the interlobar fissures. In places, as on the left side, their centres are occupied by lighter areas; these correspond with cystic spaces, containing clear fluid. It is noteworthy that although many of the shadows are of extreme density, the nodules producing them were not calcified, but very vascular.

At the apex of the left upper lobe the inner margin is thick and opaque, and beneath it is an ill-defined area of light density (corresponding to fibrosis at autopsy).

The lower and inner angle of the right lower lobe is occupied by a small homogeneous opacity.

Scattered throughout both lungs are small circular densities generally under 2 mm. diameter.

At the carina are two light shadows due to enlarged but non-calcified lymph nodes.

Radiogram of thorax (cadaver). The supraclavicular regions show no obvious lesions.

There is a diffuse homogeneous shadow of light density throughout the right thorax, the pleural cavity of which contained fluid at autopsy.

On the left side several circular but ill-defined shadows are seen, in some of which a lighter central area can be detected.

Fig. 9. (*a*) *Radiogram of Excised Lungs.* (*b*) *Radiogram of Thorax.*

Case 17. S.W., coloured female, aged 49. Died with manifestations of broncho-pneumonia following paraplegia.

Autopsy. The brain and spinal cord showed no gross macroscopic lesions.

Lungs. Right. At the base of the lower lobe was an irregular deeply pigmented area of fibrosis, 3 × 3 × 2 cm., containing two stony hard calcareous nodes, the larger of which measured 1·2 cm. diameter, and several small gritty foci in the neighbourhood. Beneath this was a breaking down, necrotic caseous focus, 5 × 5 × 4 mm., extending to the pleura, which at this point was thickened and adherent to the diaphragm. Along a line extending from this area to the hilum were two calcified intra-pulmonary parabronchial lymph nodes; the smaller, 0·5 cm. diameter, was situated about 5 cm. deep to the hilum, and the larger, 2 × 2 × 1 cm., almost at the hilum. The inner third of this lobe was the seat of considerable congestion and patchy broncho-pneumonia.

Left. In the lower lobe and near the interlobar fissure was a densely calcified focal nodule, 0·5 cm. diameter, and along a line extending from it to the hilum was a calcified intra-pulmonary lymph node 2 cm. in diameter. The inner thirds of both left lobes were congested and somewhat oedematous.

No lesions were found at the apices of the upper lobes.

Below and to the right of the bifurcation of the trachea was a completely calcified extra-pulmonary lymph node measuring 3 × 2 × 1 cm.

Radiogram of excised lungs. The inner third of the right lower lobe field is occupied by a diffuse opacity, and the inner half of the left side by a diffuse mottling of lighter density.

In the lower half of the right lung field is a small group of shadows of extreme density, and along a line from these to the hilum are three opacities of similar density, the upper two of which are large and circular.

On the left side, lying below the interlobar fissure, is a small circular opacity; and above this at the hilum is another but larger shadow, produced by a calcareous lymph node.

Several minute focal densities are also seen scattered throughout other parts of both lung fields.

Radiogram of thorax (cadaver). The shadows produced by calcified lymph nodes, and by calcified lesions in the lung tissue over 0·5 cm. diameter, are well defined.

On the right side, just above the diaphragm and beneath the eighth rib, is a small group of shadows identical with those seen in the radiogram of the excised lungs. The shadow at the hilum, produced by a calcified lesion in a tracheobronchial lymph node draining this area, is also clearly defined.

On the left side and above the seventh rib is a well-defined opacity produced by a calcified pulmonary lesion, 0·5 cm. diameter, and the nearest lymph node is represented by a larger and denser opacity at the hilum, part of which is seen sharply defined through rib and heart shadows.

Mottling due to congestion is seen, but contrasts rather poorly with the normal lung field, as compared with that seen in the radiogram of the excised lungs.

The close relation of focal pulmonary lesions with those of the nearest chain of tracheobronchial lymph nodes is well illustrated in this case.

Fig. 10. (*a*) *Radiogram of Excised Lungs.* (*b*) *Radiogram of Thorax.*

Case 29. H. S., white female, aged 49. Admitted for carcinoma of cervix. No history of chest disease. Died after hysterectomy.

Autopsy. Lungs. Right. The pleura was thickened and densely adherent to the chest wall and diaphragm. The interlobar fissures were obliterated. Both lobes were considerably oedematous.

The upper 6 cm. of the right upper lobe was tough and deeply pigmented. The cut sections showed numerous fibrous strands, and near the posterior aspect were a number of pigmented, dense fibrous nodules, many of which were calcareous in their centres. The lowest and largest of this group measured 1·5 × 1 × 1 cm., and contained caseous nuclei of mortar-like consistency. A few smaller subpleural nodules were seen in other parts of this lung, and one, just above the base of the middle lobe, was 0·5 cm. diameter and partially calcified.

Left. The pleura over the apex of the upper lobe was very much puckered. The subjacent lung tissue occupying the upper 6 cm. of the upper lobe was deeply pigmented and intersected by numerous fibrous strands, along which were a large number of pigmented nodules of fibrosis. Many of these were caseous and some partially calcified, and varied in size up to 6 × 5 × 5 mm. Some were at the extreme tip, and many beneath the pleura of the posterior aspect. Above the base of this lobe was a small fibrotic nodule, and lying in the anterior free border was a stony hard calcareous node, 7 × 5 × 4 mm. The cut surface of the upper lobe, apart from the lesions described, was dry and moderately well aerated. The lower lobe was congested and oedematous.

The tracheobronchial lymph nodes were not noticeably enlarged. Beneath the beginning of the bronchus, going to the base of the left upper lobe, was a small intra-pulmonary node whose centre contained gritty caseating material. Beneath the left main bronchus was a stony hard extra-pulmonary node, 2·5 × 0·5 × 0·5 cm., and completely calcified.

Radiogram of excised lungs. The normal lung markings on the right side are obscured to a great extent by a diffuse mottling. At the apex of the right upper lobe are a number of irregular shadows of varying density. Two smaller shadows are also seen in the mid zone of the right lung field.

The margin of the upper part of the left upper lobe is irregular. Beneath the outer part of this margin are a considerable number of irregular but sharply defined opacities. These appear to have a radial arrangement along lines

converging from the periphery toward the hilum. Near the lower and inner angle of the left pulmonary field is a dense circular opacity, 7 mm. diameter, corresponding with a lesion found in the anterior lappet of the upper lobe.

Although these shadows accurately correspond with calcareous and caseous parts of the lesions found at autopsy, the non-calcified fibrous zones are not clearly recognizable in the radiogram.

The outer and lower part of the left lung field is occupied by a diffuse homogeneous shadow resulting from oedema of the left lower lobe present at autopsy.

Beneath the termination of the markings of the left main bronchus is a small density, and below and to the left of the carina is a much larger, denser, and crenated shadow.

Radiogram of thorax (cadaver). In the right supraclavicular region a small group of densities is seen between the third and fourth ribs. A small shadow is seen through the fourth rib below the clavicle. The lesions near the tip and inner aspect of the apex are covered by the inner ends of the first and second ribs, and the transverse processes of the corresponding vertebrae. In addition to the heavier densities, the right supraclavicular zone shows an irregular mottling of light density. The upper part of the infraclavicular zone is occupied by a diffuse homogeneous shadow, and at the level of the sixth rib anteriorly is a faint horizontal line indicating fibrous obliteration of the fissure between the upper and middle lobes.

On the left side a number of small densities in the supraclavicular region, and one between the third and fourth ribs just below the clavicle, may be recognized. The smallest of these opacities seen between the third and fourth ribs was probably produced by a calcareous nodule 3 mm. diameter. A number of very dense shadows up to 6 mm. diameter, seen in the radiogram of excised lungs and produced by lesions just beneath the tip of the apex, are covered by the upper two ribs. At the level of the upper border of the left eighth rib, is a well-defined circular density. This, as previously observed, was due to a lesion in the upper lobe.

Some generalized mottling of a light density is seen in the left supraclavicular zone, and the whole of the lung field below is occupied by a diffuse opacity.

The hilar shadows are greatly increased, and it is of interest to note that at autopsy most of the tracheobronchial lymph nodes were not enlarged, and that oedema and congestion were the only pathological changes found in this region. The one calcified node found below the left bronchus cannot be recognized in the chest plate.

Among the interesting points illustrated by this case, those particularly noteworthy are:

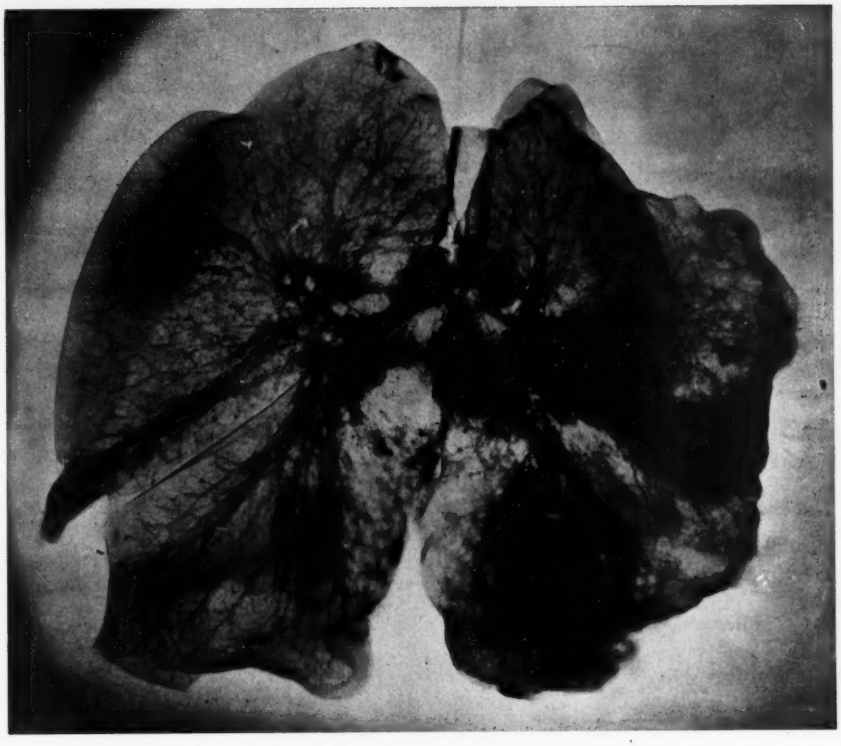
1. The difficulty of demonstrating in the radiogram of the thorax, lesions beneath the apical pleura so often found at autopsy, even when they are heavily infiltrated with calcium.

2. The poor and ill-defined shadows produced by simple fibrous tissue except when it is dense in character.

3. The large hilar shadows, notwithstanding the absence of peribronchial fibrosis or enlargement of tracheobronchial nodes.

4. The relation of pulmonary lesions to pathological changes of the lymph nodes. Although the apical zones of both lungs showed most extensive pathological change, the lymph nodes draining these areas were free from disease: the nodes draining the area at the base of the left upper lobe containing a healed lesion were pathological.

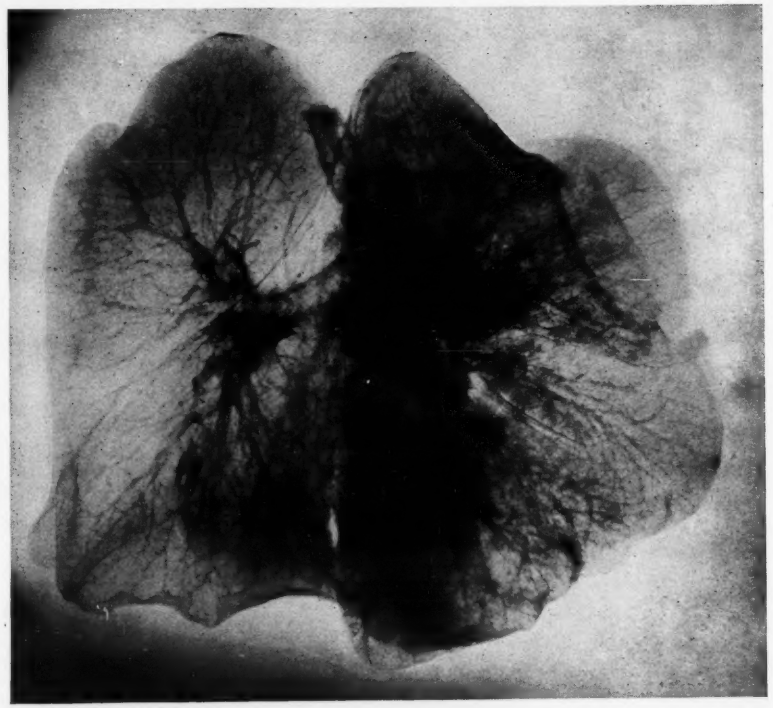
5. The left upper lobe may extend down as low as the eighth rib anteriorly.



Left FIG. 1 *Right*



Right FIG. 2 *Left*

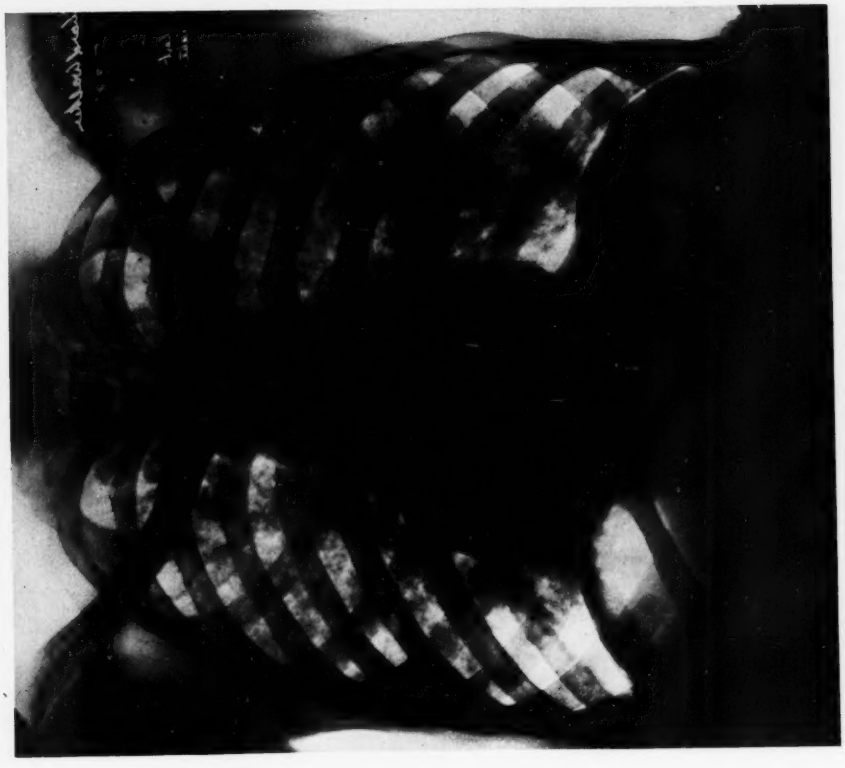


Left FIG. 3 *a* *Right*



Right FIG. 3 *b* *Left*





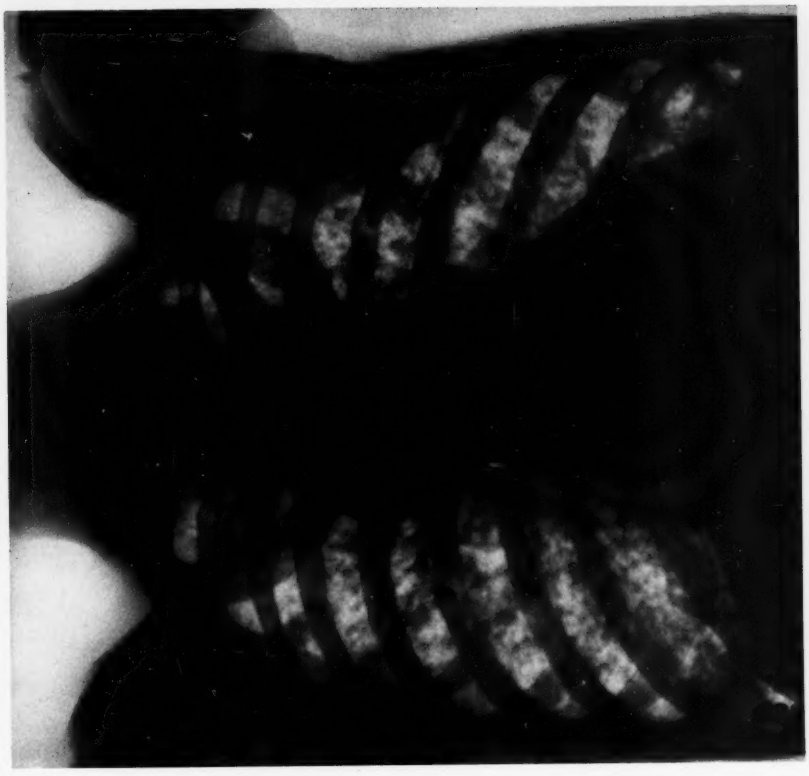
Right Left

FIG. 4 b



Right Left

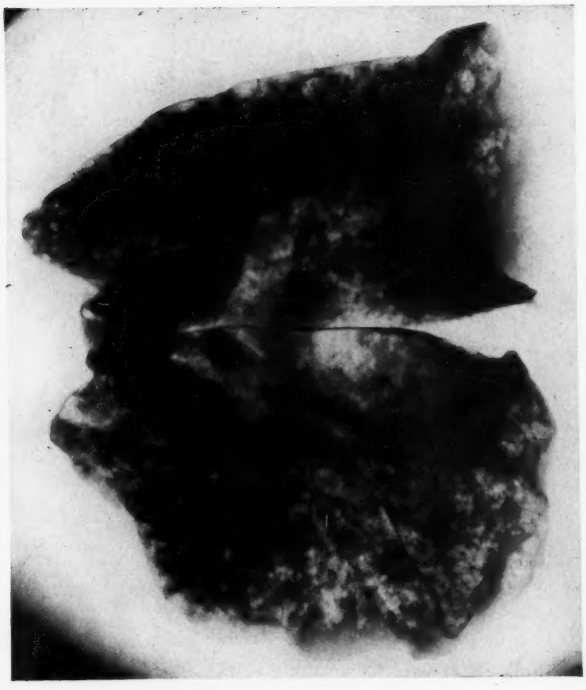
FIG. 4 a



Left

FIG. 5 b

Right



Left

FIG. 5 a

Right



Right FIG. 5 *c* *Left*



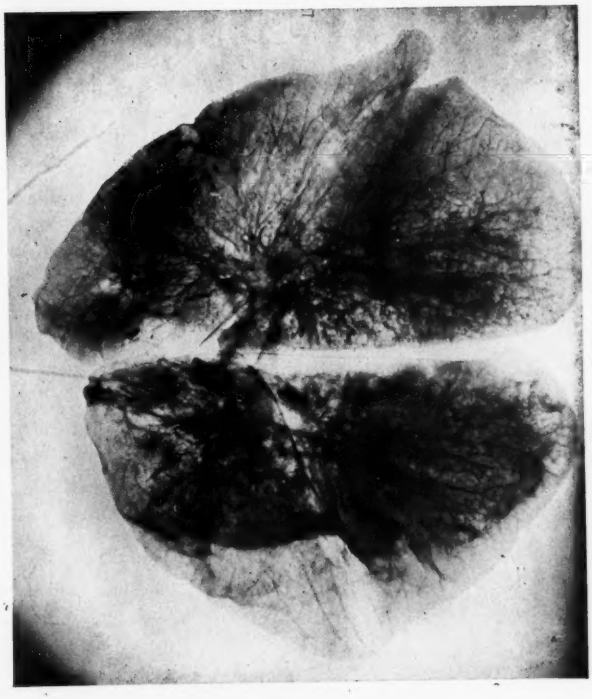
Right FIG. 6 *Left*





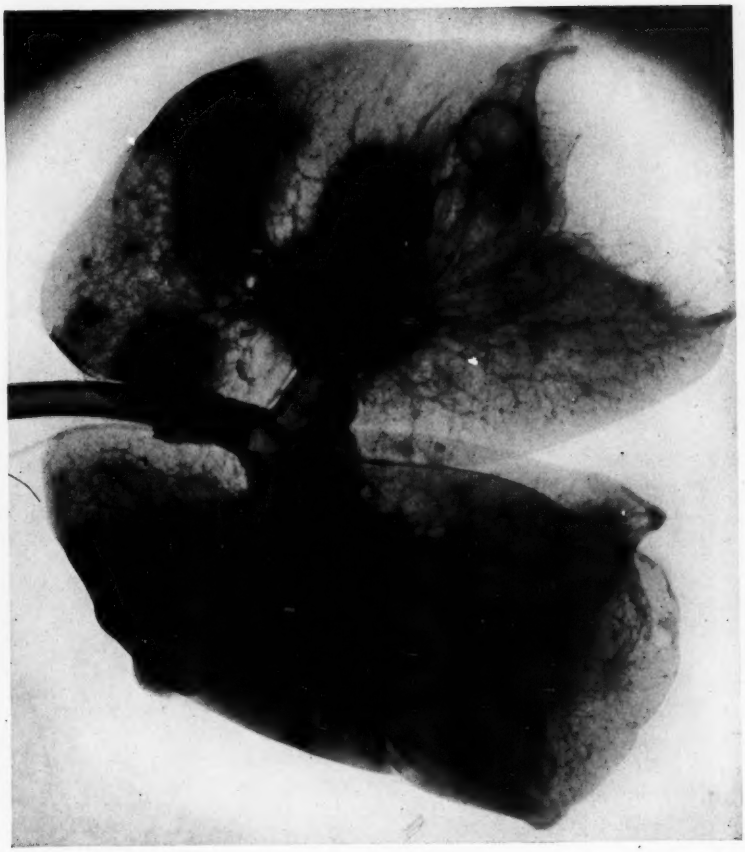
Left Right

FIG. 7b



Left Right

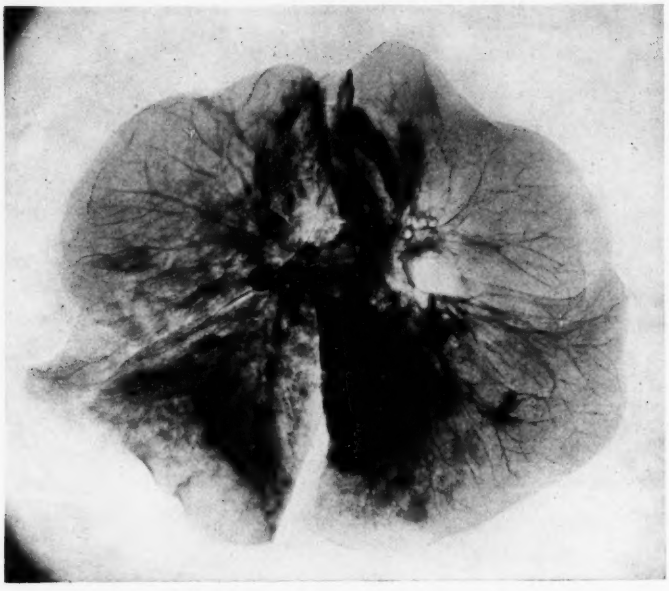
FIG. 7a



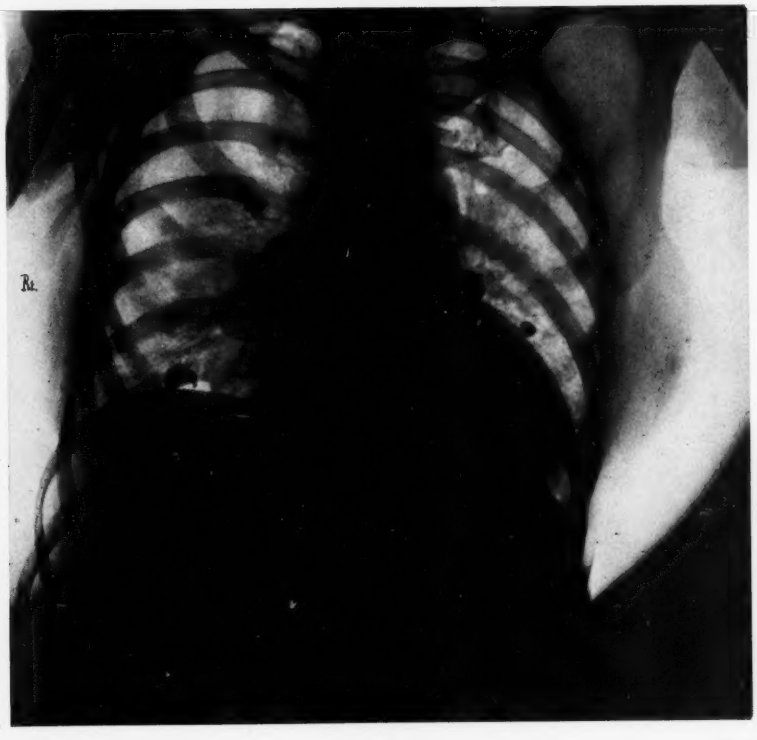
Left

FIG. 8

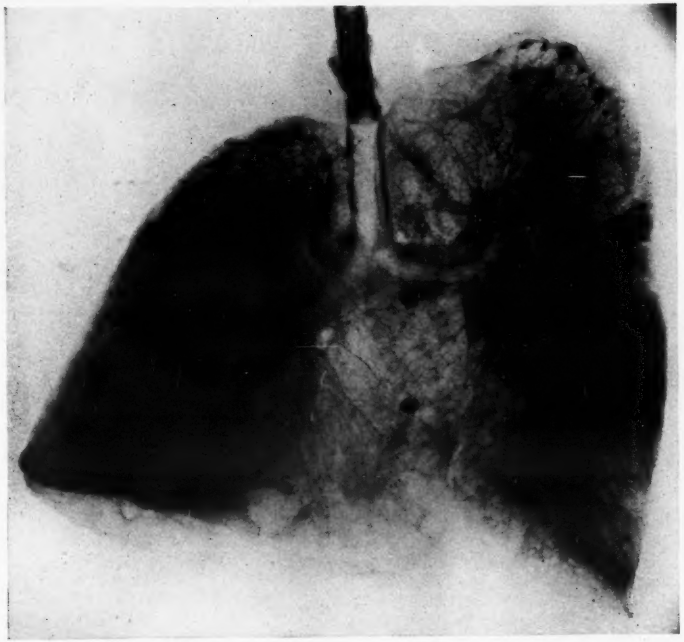
Right



Left FIG. 9 *a* *Right*



Right FIG. 9 *b* *Left*



Right FIG. 10 *a* *Left*



Right FIG. 10 *b* *Left*

SUPRARENAL VIRILISM[1]

WITH A REPORT OF TWO CASES

By A. DINGWALL FORDYCE

PATHOLOGICAL NOTES

By W. HOWEL EVANS

(From the Royal Liverpool Children's Hospital)

With Plates 27–32

During the past eight years I have met with six cases of primary tumour of the suprarenal gland. Four of these were cases of malignant medullary growth—neuroblastoma—three being of the Hutchison type and one of the Pepper type. The remaining two cases were those of cortical hypernephroma—suprarenal virilism—here described.

In both cases Professor Ernest Glynn studied the children during life, and to him, in the first place, were entrusted the tumours removed and, in the case of death, the post-mortem specimens. From many conversations with him after his preliminary examinations it was clear that he was in no doubt that the tumours in these two cases were of cortical origin and similar to those previously described by him in association with suprarenal virilism.

Professor Glynn's authoritative opinion carries great weight, but unfortunately he has been prevented from sharing in the report as here presented and many notes which were in his charge have not been available.

Case I.

J. H., male, born February 1925, died May 31, 1927. First seen February 4, 1927.

While attending another member of the household, Dr. A. G. W. Owen, of Birkenhead, saw this child and, recognizing a marked peculiarity, asked the mother to bring him to see me. This was only reluctantly agreed to, because the parents were 'ashamed for the boy'. This feeling of shame had been with them since he was a little baby and consequently he had been kept as secluded as possible. The family history was entirely negative and the father and mother healthy and strong. The family comprised, in addition to the patient, three other children—all quite normal and healthy—a girl aged ten years, a boy aged seven years, and a baby boy aged four months. There had been no miscarriage and no children had died.

[1] Received February 1, 1929.

The mother was quite well during pregnancy and the labour was 'ordinary'. The baby was healthy at birth and was nursed at the breast for fifteen months. 'He weighed 9¾ lb. at birth and 3 stone when eight months old.' 'He never ailed, and became fat, big, and strong.' At about the age of six months the mother noticed that there was hair on his pubis and that his penis was very big. At the age of eight months a 'rash' was noticed on his back, which persisted and gradually spread.

He always had a 'high colour' and a deep-toned voice. He was always strong and crawled about freely, but he did not walk until he was about twenty months old. Soon after beginning to walk he carried a bucket of coals weighing 18 lb. across the room. For some time, near the end of his second year, he had been losing weight.

When examined on May 15, 1927, he weighed 2 stone 10 lb., height being 2 feet 10 inches, and age two years and three months. He possessed vivid red hair and was of a most rubicund complexion (Pl. 27, Fig. 1). He was shy and ashamed of being examined and wept beneath the bedclothes. He was, however, otherwise peculiarly self-controlled. His cry consisted of a curious bellow—deep-toned but not loud—rather restrained and quiet. He did not talk. His body was covered generally with downy hairs, with coarse hair on the chin, upper lip, cheeks, breast, axillae, and pubis. There were comedones on the face and seborrheic dermatitis on back, shoulders, and chest. He was constantly dribbling urine, and the urine contained a trace of albumin, but no other abnormality was detected.

X-ray examination disclosed normal ossification for his age. A fine generalized tremor was present, the deep reflexes were brisk and equal on the two sides.

The respiratory and cardio-vascular systems appeared normal and the blood-pressure was, systolic 80 mm. Hg, diastolic 50 mm. Hg. Palpation of the abdomen revealed no abnormality except that the spleen was palpable a finger-breadth below the left costal margin. X-ray examination of the abdomen revealed no abnormality.

The external genitalia were extraordinarily developed, both testicles being large, and in the scrotum and the penis being as large as that of an adult man (Pl. 27, Figs. 1 and 2).

A diagnosis of left cortical hypernephroma was made and he was at length admitted to hospital for operation. At operation (30.5.27, by Mr. R. Craig Dun) an encapsuled tumour the size of a small orange was found in the position of the left suprarenal capsule and not attached to the kidney. This was removed, but the boy died within twelve hours after the operation.

Pathological Report.

The tumour removed at operation (Pl. 31, Fig. 3) resembled the normal suprarenal capsule in shape, weighing 66 grm. and measuring 6 cm. × 4·4 cm. × 3·4 cm. It was firm in consistency and enclosed in a thin, tough, fibrous capsule. On section it was generally dull red in colour, with a number of small bright yellow areas, especially towards the centre. A small nodule of solid tissue, bright yellow in colour and approximately 1·4 cm. in diameter, projected from the upper pole.

Histological examination. Pieces examined fresh by the bichromate method failed to show any chromaffin tissue, and no cells resembling those of the medulla were found in any of the sections examined.

The tumour consisted of a very uniform mass of cells which closely resembled those of a normal suprarenal cortex in the resting or unloaded state. They were arranged in columns or cords of varying thickness, usually narrow, separated by rather numerous thin-walled blood-vessels (Pl. 28, Fig. 4). The average size of the

cells was from 12 to 15 μ and that of the nucleus 5 to 7 μ. Occasional scattered cells and small groups of cells were larger, up to 20 μ, and of the typical 'foamy' appearance suggestive of cholesterol or other lipoid. Mitoses were very scanty, and multinucleated or giant cells, so frequently described in these tumours, were not observed. Examined by polarized light a small quantity of doubly refractive material was seen, but in sections stained by Sudan III practically no fat could be demonstrated, and sections treated with Moleschott's sulphuric acid as recommended by Boyd (1), were negative for lipoid. Chemical examination of a slice through the entire thickness of the tumour gave 1·2 per cent. of cholesterol and cholesterol ester per wet weight, or distinctly below the normal average of the suprarenal cortex.

Many parts of the tumour showed small haemorrhages and also considerable areas of necrosis (Pl. 28, Fig. 5).

Histologically the arrangement of the cells in this primary growth closely resembled that in Gordon Holmes's case (2) (1925) described by Glynn, the sections of which have been accessible to me. The cells actually are somewhat smaller, and also less 'foamy', but the similarity of the arrangement in narrow cords separated by numerous capillaries is striking. It is interesting that Glynn considered the histological appearances in Gordon Holmes's case 'the least atypical yet described', and in that case the recovery of the patient showed that secondaries did not develop. In the present case, however, the tumour, despite its histological resemblance to Holmes's tumour had already given rise to metastases at the time of the operation.

Necropsy.

The necropsy was made by Professor Ernest Glynn. The operation area was normal and no trace of a left suprarenal was found. Further, no right suprarenal capsule could at first be found, but after considerable search, two small yellowish nodules were discovered in the fat above the upper pole of the right kidney. The larger measured $1 \times 1 \times 0{\cdot}75$ cm., the other was about 2 mm. in diameter. Subsequent histological examination showed these to consist entirely of normal suprarenal cortex, no chromaffin tissue being demonstrable.

Kennedy and Lister (3) (1927) have already called attention to the fact that in their case and in that of Hijmans van den Bergh (4) (1915) somewhat similar abnormality of the opposite suprarenal was found. In all three cases the patient died unexpectedly shortly after the operation.

Two metastases were found, in the liver and the brain.

Liver: a circumscribed oval-shaped metastasis was found on the under surface of the left lobe. It measured 4·5 cm. and 2·1 cm. in its longer and shorter diameters. Its colour was deep yellow, mottled with reddish haemorrhagic areas. Histologically this secondary deposit was rather less 'typical' than the primary growth. In certain areas a similar arrangement in narrow cords separated by blood-vessels of cells resembling the suprarenal cortex could be seen, but in other parts there was considerable variation. Thus occasional multinucleated cells were present and some parts presented a pseudo-papilliferous arrangement from central necrosis (Pl. 28, Fig. 7). The nodule was also distinctly more vascular than the primary growth, and there were numerous haemorrhages. Chemical examination showed 0·504 grm. per cent. of cholesterol and cholesterol ester per 100 grm. wet weight.

Brain: a further solitary circumscribed metastasis was found in the middle of the left superior frontal gyrus. It measured $1{\cdot}6 \times 1{\cdot}2 \times 1$ cm. and was deep red in colour, with a number of small greyish areas.

This tumour was the most vascular of the three, presenting an enormous number of thin-walled capillaries. Haemorrhages, however, were very few. Apart from the vascularity the cells showed a close resemblance to those of the

primary suprarenal tumour in arrangement, size, and staining. No multinucleated cells were present.

No other metastases were found.

Testes: average weight, with epididymis 2·36 grm. and therefore not grossly enlarged. (The testes of a boy aged 24 months who died from bronchopneumonia shortly after this post-mortem averaged 2·6 grm. The average weight of the testis without epididymis in thirteen cases between 2 and 3 years was 1·71 grm.: private communication from Professor H. M. Turnbull.)

Smears from the freshly cut gland and from the seminal vesicles showed no spermatozoa. Histologically the testis (Pl. 28, Fig. 6), both as regards the seminiferous tubules and the interstitial cells of Leydig, showed the normal resting stage of the gland at this age (see Mott (5), 1919), there being no evidence of spermatogenesis and the interstitial cells being very scanty. The conclusion was that the gland was about normal for the age and showed no evidence of secretory activity.

The *thyroid* was not obviously enlarged, and sections showed it to be hyperaemic, with the epithelium rather columnar and hyperplastic, and colloid deficient. A similar appearance was noted by Glynn in Dun's case (6) (1911).

Parathyroids: four were present, the left lower gland being somewhat larger than normal—12 mm. × 9 mm. × 6 mm., the others approximately 3 mm. in diameter. Histologically all four were normal.

Thymus: weight 13 grm., i.e. somewhat below normal. It was entirely glandular and showed no signs of involution.

Pituitary: normal macroscopically and microscopically.

Pineal: noted as macroscopically normal, no section.

Prostate: weight 5 grm. Microscopically the acini were scanty and simple, and the fibrous tissue and plain muscle in excess. It was clearly not a functioning gland.

Mesenteric glands: a few caseating lymphatic glands in relation to the middle of the small intestine were found; apart from this there was no other abnormality present.

Conclusion.

From the anatomical position, naked eye and histological appearances, including the resemblances to previously described similar growths, there is no doubt that the main tumour was one of the suprarenal cortex. It is to be observed that no chromaffin tissue could be recognized in the suprarenal representatives on either side of the body. The occurrence of metastases is of interest, especially in view of the 'typical' nature of the cells of the primary growth. Many of these tumours are malignant, but the development of malignancy is usually slow. The undeveloped state of the testis is in agreement with previous reports as under:

Author.	Date.	Age.	Condition of Testes.
Linser (7)	1903	3	'Testes and epididymis somewhat larger than pigeon's eggs. Microscopically the testicular tubules contain only here and there well-formed sperms . . . in short the whole picture is that of a non-functioning testicle.'
Adams (8)	1905	16	No information.
Guthrie and Emery (9)	1907	$4\frac{3}{4}$	'Testicles of size and degree of development normal to a boy of this age. No spermatozoa in sections of testis and epididymis or in fluid from seminal vesicles.'
Baldwin (10)	1914	$5\frac{10}{12}$	'Testicles normal for boy of his age . . . small and not completely descended.'
Tschernobrow (11)	1919	11	'Moderately hypoplastic.'

Clearly, therefore, in these cases occurring in young boys, the 'virilism' is not associated with sexual precocity in the sense of *potency*.

Case II.

E. B., female, born July 1925, first seen July 18, 1927, at the age of 2 years (Pl. 29, Fig. 8).

She was brought to the Out-Patient Department on the advice of a nurse who considered her appearance abnormal. There was no complaint on the part of the mother, but she stated that the child was constipated and had frequency of micturition. The family history disclosed nothing of note, and the father and mother are both alive and healthy. There was one other child, a boy aged 4 years, who was alive and well. There had been no miscarriages and no children had died. The pregnancy and labour were 'normal'.

Notes on examination. She was a red-haired child with a vivid complexion and a rather precocious frowning expression. She could talk, but was not responsive and quickly displayed temper. There was a slight growth of downy hair on the upper lip; no comedones were present.

The abdomen was distended and a large tumour was palpable, occupying the whole of the left abdomen and extending beyond the midline. The respiratory and cardio-vascular systems were normal.

The labia were very large and a much enlarged and hard clitoris protruded to a distance of more than 3 cm. (Pl. 30, Fig. 10). There was a muco-purulent vaginal discharge, and a catheter specimen of urine contained *B. coli* and pus. There was a profuse growth of coarse red hair on the pubes and labia. A blood count showed red cells 4,000,000, white cells 6,500, haemoglobin 80 per cent.; blood-pressure, systolic = 85 mm. Hg, diastolic = 60 mm. Hg. Ophthalmoscopic and X-ray examination negative.

A diagnosis of left cortical hypernephroma was made and the child admitted to hospital for operation.

At this time the clitoris measured 3·25 cm. in length. by 1·3 cm. in width, and the hirsuties was as follows:

Mons veneris. The growth consists mainly of short downy hairs lying flat and averaging about 1 cm. in length. A much smaller number of coarser hairs—probably not more than twelve to eighteen in total number, the three longest measuring 3·5 cm., 3·2 cm., and 3·0 cm.

Labia majora. A profuse growth mostly of coarse hairs. The majority average about 2 cm. in length, and the three longest measure 3·5 cm., 3·5 cm., and 4·0 cm.

Axillae. Nil.

Upper lip. Downy hairs less than $\frac{1}{2}$ cm. in length.

On 9.8.27 the large tumour was removed by Mr. W. A. Thompson. The child made an uninterrupted recovery from the operation and left hospital 8.9.27 in good health. Before leaving it was noted that she was more baby-like, played more with toys, talked more and had a better temper.

After leaving hospital her health continued good. She was 'not so shy—happier than she used to be'. By the end of the year (1927) there were no coarse pubic hairs, only a few short downy hairs on the pubis and not more than four or five coarse hairs on the labia. The clitoris was distinctly smaller.

She has continued in good health since and has gained normally in height and weight. She plays naturally with other children and discloses no peculiarity.

On 4.9.28 there were no hairs on the upper lip or on the mons veneris and only a few slight downy hairs on the labia majora. The clitoris measured 2·5 cm. by 1 cm. (Pl. 29, Fig. 9 and Pl. 30, Fig. 11).

On 1.11.28 her height was 3 feet and her weight 31 lb. 2 oz. (age $3\frac{4}{12}$ years).

She was last seen on 11.12.28 and was in excellent health. A healthy boy

was born to the mother in August 1927, and both this boy and the elder brother continue healthy. Neither of the boys has red hair.

Pathological Report.

The operation specimen (Pl. 31, Fig. 12) weighed, before fixation, 1,500 grm. It was oval in shape, measuring 14 and 11 cm. in its longer and shorter diameters. It was enclosed in a smooth, tough, fibrous capsule. On cutting it across, the tumour showed a narrow outer zone of solid tissue, some parts being bright yellow and others red, obviously from haemorrhages, and a larger central part, comprising fully five-sixths of the bulk. The central part consisted of a number of large cystic spaces or loculi bounded by thin strands of connective tissue, and containing a glairy mucoid fluid, much of which escaped on sectioning. A few islands of the solid red and yellow tissue extended towards the centre.

Histologically the tumour can be divided from without inwards into several well-defined zones or layers, which are shown in Pl. 32, Fig. 13, lettered from A to G. First there is the fibrous capsule of what appears to be the suprarenal gland itself (A), and immediately beneath this (B) a narrow layer of rather compressed cortical cells resembling those of the normal zona glomerulosa. Immediately internal to this layer is a further capsule (C) of fibrous tissue limiting the tumour proper. The outermost layer of the tumour is composed of another narrow band of typical cortical cells (D) averaging 13 to 15 μ, nucleus 6 to 7 μ, which abruptly merges into a much wider layer or zone of larger cells of grossly 'foamy' appearance (E). These last cells comprise the bulk of the cellular portion of the tumour. Their average size varies between 30 and 40 μ, the nucleus 10 to 15 μ (Pl. 32, Fig. 14). In the centre of the tumour these large cells show progressive degrees of degeneration and necrosis (F), and finally the central part, as already mentioned, is almost completely necrotic (G). The arrangement just described could be shown in pieces taken from several points on the circumference of the tumour.

The arrangement of the tumour cells generally resembled that in Case I, but the cell columns were usually broader. The stroma was very scanty, thin-walled blood-vessels were numerous, and in many places there were considerable haemorrhages. Occasionally strands of smaller cells, less 'foamy' in character, arranged in columns like the zona fasciculata were interspersed between the columns of the large cells. Multinucleated cells were absent and mitoses scanty. The description agrees fairly closely with that of the suprarenal tumour in Kennedy and Lister's case. In that case a metastasis was found in the lung.

No chromaffin tissue could be demonstrated in any of the numerous sections examined. Examined by polarized light a considerable amount of doubly refractive material could be detected in the cellular zone, but practically none in the central cystic part. Chemical investigation showed that the outer cellular part contained 1·77 grm. of cholesterol and cholesterol ester, the inner degenerated portion 50 mg. per cent. only. The large foamy cells gave an intense brownish purple reaction with Moleschott's sulphuric acid, and also contained a large amount of material staining orange with Sudan III.

The tumour is thus as it were encapsulated within the suprarenal gland, and the appearances leave no room for doubt that it is another example of a tumour of the suprarenal cortex.

Discussion.

On the subject of this paper a very considerable literature has developed, and long lists of reference are given in the papers of Glynn (12) (1912 and 1921),

Tschernobrow (13) (1919), Berner (14) (1923), Collett (15) (1924), Krabbe (16) (1924), Rolleston (17) (1925), Moggi (18) (1925), Parkes Weber (19) (1926), and Crosby and Smith (20) (1928).

Tumours of the gonads may produce true hypergenitalism, and some tumours of the pineal produce marked changes in the secondary sex characters.

The most striking symptom of a cortical hypernephroma is the change in secondary sex characters.

Cases of cortical hypernephroma or of hyperplasia of the suprarenal cortex produce secondary sex changes which vary according to the age of the individual.

Hoskins (21) recognizes three groups of suprarenal hypergenitalism, namely:

1. Hypertrophy during foetal life, producing pseudo-hermaphroditism.
2. Hypertrophy during early post-natal life producing pubertas precox.
3. Hypertrophy after puberty, producing virilismus or hirsutismus.

Gallais (22) described four age-groups and Apert (23) five. It appears, however, inadvisable to multiply such groups, and Glynn preferred to include forms at all ages under the name of suprarenal virilism.

Glynn and others regard the sex changes as secondary to hyperactivity of the cortical function, others regard the result as that due to a pluri-glandular disturbance, while Krabbe holds that there is no proof that an internal secretion from the cortex of the suprarenal plays a special role on sex organs. He says: 'La glande génitale, chez les embryons mâles, est toujours purement testiculaire, tandis que la même glande, chez les embryons femelles, est bissexuée et consiste en une partie ovarienne externe et une partie testiculaire interne; c'est celle-ci qui touche l'ébauche de l'écorce surrénale. C'est dans ce second fait que nous allons trouver l'explication du virilisme chez les femmes et les petites filles à tumeurs surrénales, en ce que nous trouvons qu'il n'est pas improbable que ces tumeurs se trouvent développées, en effet, aux dépens des éléments de la portion testiculaire de l'ovaire fœtal'. The sex changes produced consist in masculinization of the female, and in the case of the male intensification of the male characteristics, with however, in the case of young boys, no potency—actual sex-power developing only slowly.

Glynn, 1912, writes: 'In children and young adult females where the sex abnormalities are acquired there is usually unilateral malignant cortical neoplasia. . . . In pseudo-hermaphroditism the sex abnormalities are mainly congenital and the adrenal lesions, if any, are bilateral cortical hyperplasia or cortical rests. . . . Rests from the adrenal cortex are common in certain localities, especially in infancy, except in the kidney. They are usually of minute size, and are not associated with sex abnormalities, unless there is much enlargement, when such may sometimes occur in pseudo-hermaphrodites.'

Weber and others have noted the fact that similar sex changes to those occurring in cases of true hypernephromata of the adrenal cortex occur sometimes in the absence of discoverable cortical abnormality, while Mathias (24) says:

'Indessen soll eine erhebliche Lücke unserer Kenntnisse keineswegs verschwiegen werden. Zwischen Hypernephromen mit den geschilderten Wirkungen [i. e. sex changes] und solchen, welche nur die Potenz des eigenen Wachstums besitzen, liessen sich bisher keinerlei Unterschiede feststellen'. There are, for example, many women with adenomatous knots in the cortex of the suprarenal who do not display excessive hairiness or a beard, and Bittorf (25) and Parkes Weber have described cases in which males developed female attributes (lactation).

The converse of tumour growth or hyperplasia of the cortex—that is, hyperepinephry—has been termed hypo-epinephry and has in its gross forms those types described by Gilford as *progeria* and by Variot as *nanisme sénile*.

Such gross cases as those described in this paper are not common in early childhood, and successful operative treatment in them is very rare. Collett describes one very similar to Case II.

A striking feature in the aspect of my two cases was the extreme redness of the hair. Strauss (26) has stated: 'Ferner fiel mir bei der Durchsicht der Kasuistik auf, dass es sich bei den Fällen von suprarenalem Hirsutismus fast ausschliesslich um schwarzhaarige und überhaupt meist um brünette Personen gehandelt hat, was zu interessanten Betrachtungen über Pigmentfragen Anlass geben kann'. In the cases of Fawcett, Hadfield, and Phillips (27) and of Kennedy and Lister (28) the hair was noted as black; Ratner (29) speaks of brunettes and Jewesses; but Gordon Holmes says of his case, 'The hair on the upper lip was straight, coarse, and brown, while that on the chin and in the area of the male beard was more reddish in colour and curly'.

It is of interest to note the configuration of the larynx in Case I (J. H.). As shown in Pl. 32, Fig. 15, it displays the characteristic deformity found in cases of congenital laryngeal stridor—namely, great exaggeration of the normal infantile peculiarities of the part, resulting in narrowing in the transverse diameter of the upper aperture of the larynx (30). I can find no record of a similar finding in cases of this kind.

The paintings and drawings which illustrate this paper are the work of Mr. D. J. Kidd, Thompson Yates Laboratories, The University, Liverpool, and I desire to thank him for the fidelity of his work.

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DESCRIPTION OF PLATES.

PLATE 27, FIG. 1. Case I. J. H., aged $2\frac{2}{12}$ years.

FIG. 2. Ditto.

PLATE 28, FIG. 4. Case I. Primary suprarenal growth showing narrow columns of cells resembling the normal zona fasciculata separated by numerous capillaries (× 220).

FIG. 5. Case I. Primary suprarenal growth showing areas of necrosis (× 110).

FIG. 6. Case I. Testis, showing absence of spermatogenesis (× 40).

FIG. 7. Metastasis in liver showing multinucleate cells and pseudo-papilliferous arrangement (× 220).

PLATE 29, FIG. 8. Case II. E. B., aged 2 years. Before operation.

FIG. 9. Case II. E. B., aged $3\frac{4}{12}$ years.

PLATE 30, FIG. 10. Case II. E. B., aged 2 years. At time of operation.

FIG. 11. Case II. E. B., aged $3\frac{4}{12}$ years.

PLATE 31, FIG. 3. Suprarenal tumour, Case I. Natural size.

FIG. 12. Case II. Suprarenal tumour (natural size).

PLATE 32, FIG. 13. Case II. Suprarenal tumour showing the successive layers of cells described in the text.

FIG. 14. Case II. Showing the large 'foamy' cells; see Fig. 13 E (× 220).

FIG. 15. Case I. Drawing of larynx in Case I.

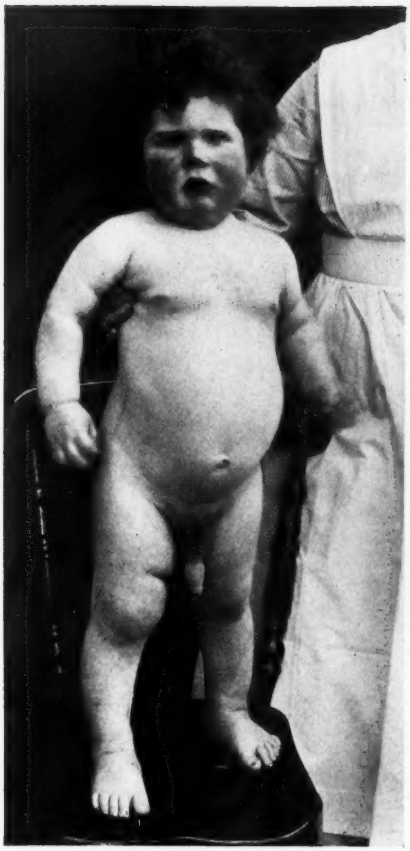


FIG. 1. J. H.—Case 1



FIG. 2. J. H.—Case 1

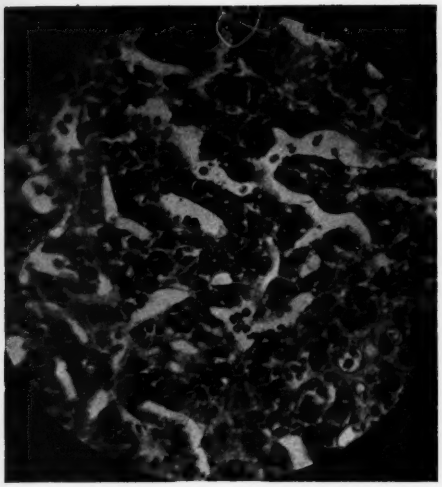


FIG. 4. Primary suprarenal growth showing narrow columns of cells resembling the normal zona fasciculata, separated by numerous capillaries. (× 220).

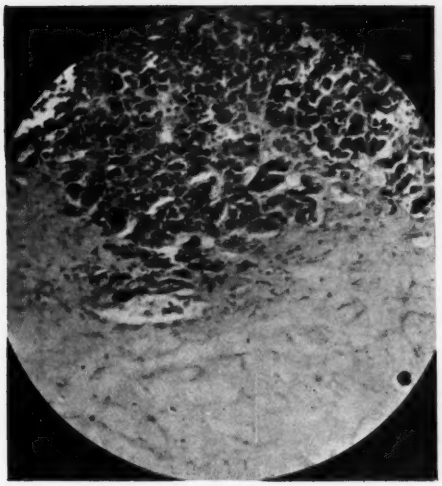


FIG. 5. Primary suprarenal growth showing areas of necrosis. (× 110).

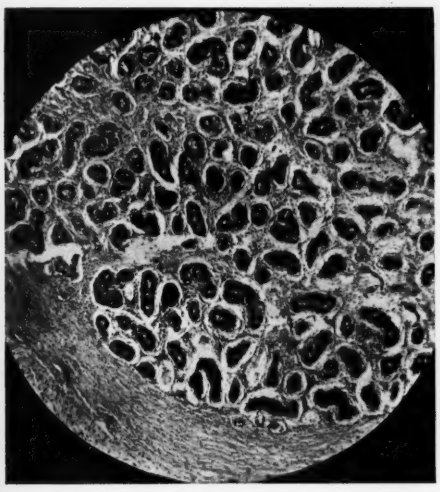


Fig. 6. Testis, showing absence of spermatogenesis. (× 40).

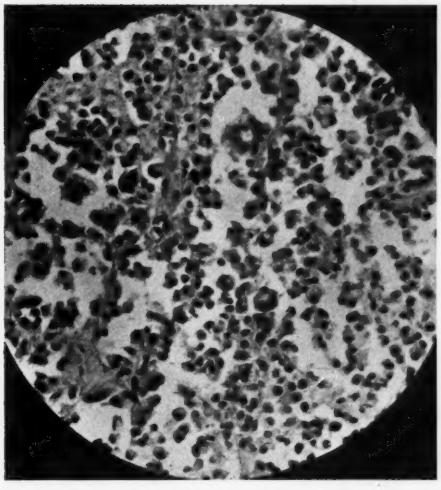


Fig. 7. Metastasis in liver, showing multinucleated cells and pseudo-papilliferous arrangement. (×220).



FIG. 8
E. B.—Case 2
July 1927 before operation



FIG. 9
E. B.—Case 2
November 1928

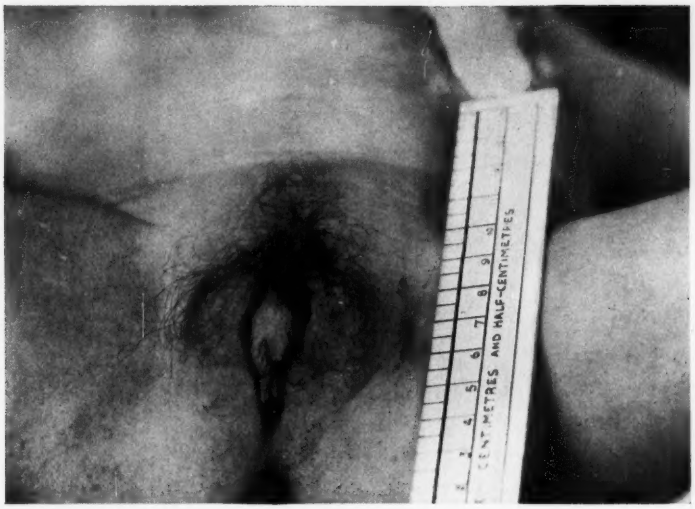


FIG. 10

E. B.—Case 2 –Genitalia before operation

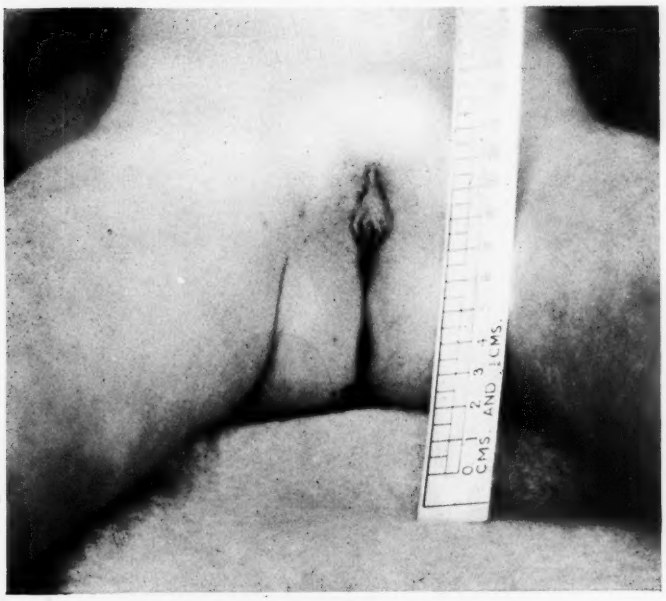


FIG. 11

E. B.—Case 2—Genitalia November 1928

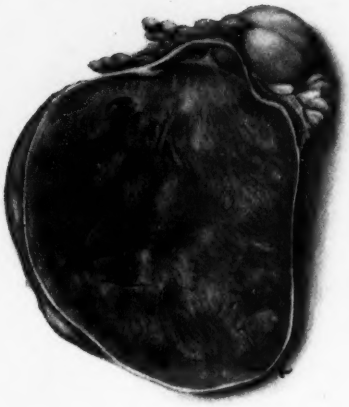


FIG. 3. Tumour on section—Case 1. Actual size.

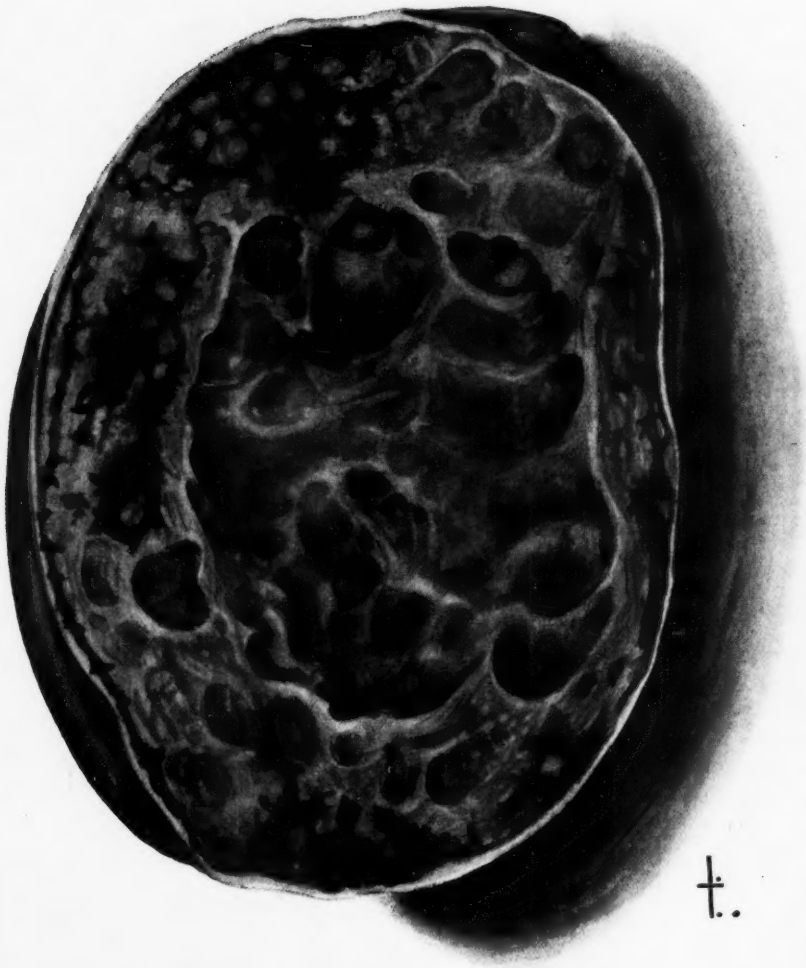


FIG. 12. Tumour on section—Case 2. Actual size.



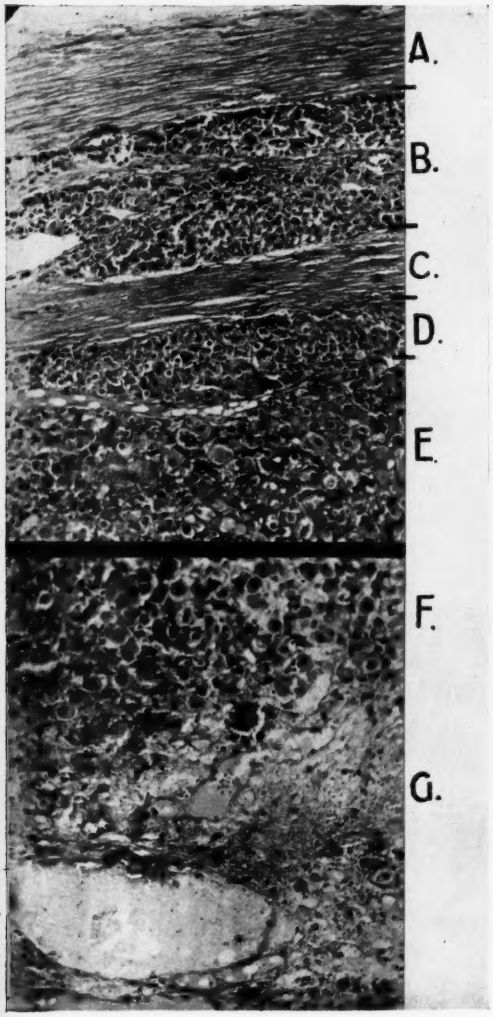


FIG. 13. Suprarenal tumour showing the successive layers of cells described in the text. (× 110).

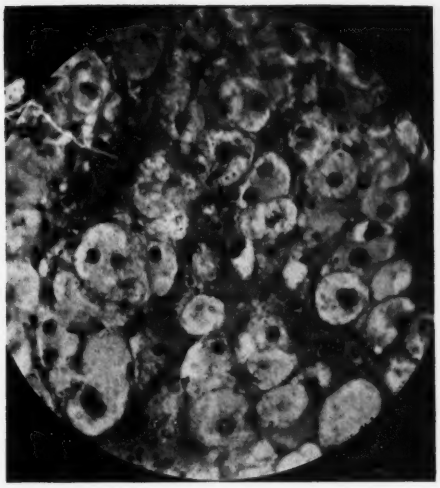


FIG. 14. Showing the large 'foamy' cells (see Fig. 13 E). (× 220).



FIG. 15

FAMILIAL POLYCYSTIC DISEASE OF THE KIDNEYS[1]

By C. J. FULLER
(From University College Hospital)

Introduction.

The fact that polycystic disease occurs in some instances as a familial abnormality is well known. Cairns (1) has recently reported a series and at the same time extracted from the literature the accounts of families similarly affected.

The present paper deals with a single family that has not been previously reported. In this instance the disease has been shown to exist through four generations in succession, whereas no example referred to in Cairns's paper has been traced beyond three generations. Moreover, it was found that no less than nine out of a total of twenty-seven individuals in the four generations of this family showed unmistakable evidence of the condition. This is a much higher proportion, 33 per cent., than has, so far as I am aware, been hitherto recorded.

The inquiry into the family originated with the history given by the patient, Case III. 5, who had been admitted to University College Hospital for abdominal pain. The majority of her relations lived in and around London, and they showed every desire to assist me in my search, so that I was able to examine personally all the living members with the exception of six. Of these latter, five were living in Australia, where, at my request, they were examined by their family doctor, who reported that no abnormalities could be detected; the sixth I was unable to trace.

The only absolute proof of the presence of this condition is the inspection of the abnormal viscera, either at operation or autopsy. This was only possible in the two cases who had died out of the twenty-seven.

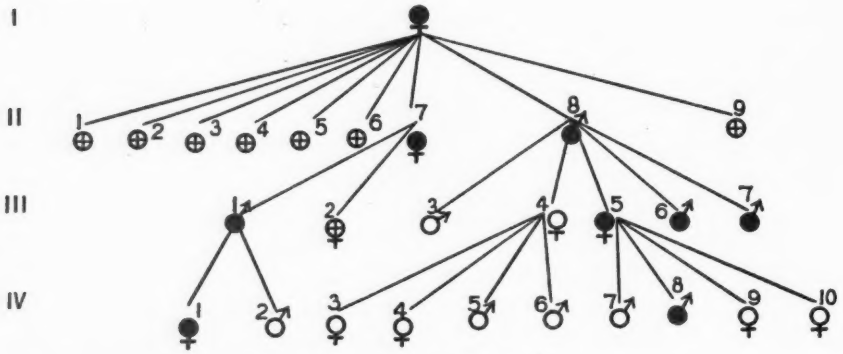
The point on which I based my diagnosis in the living was the presence of enlarged kidneys, which, in the older members of the family, were obviously nodular on the surface. Additional evidence was sought by examination of the urine for abnormalities, the impairment of renal efficiency, and a history of haematuria.

Evidence during life of polycystic disease of the kidneys turns upon progressive enlargement of the organs and associated deterioration of their functions. It is consequently less easily obtained in the first twenty years of life, and the suggestive features in Nos. 1 and 8 of the fourth generation were not yet very

[1] Received March 15, 1929.

definite. For the same reason it cannot be concluded that the other eight individuals in the fourth generation were free from latent polycystic disease, and that they would not develop its features as they grew older.

Radiograms were taken in two instances; both showed enlarged renal shadows, and in one instance there were three small opaque areas suggesting stones in the substance of the kidney. In none of the surviving cases had the condition been recognized until the present investigation, doubtless because few symptoms were present; and since the patients came up for examination at my request, I did not feel justified in subjecting them to radiographic examination of the renal pelvis, a procedure which is not infrequently accompanied by considerable pain.



● = those members of the family who are affected.
⊕ = cases about whom there is no information of the kidney condition.
○ = cases in whom there is no evidence of the condition.

Unfortunately no information is available as to the cause of death of the seven children in the second generation who died in infancy. I was, however, able to ascertain that their father died of pulmonary tuberculosis, and this infection may have some bearing on the high death-rate.

Case Reports.

Below are given the details of the individual members of the family :—

Case I. 1. Annie T. M. Born 1820. Married. 9 children. Died at the age of 53 in the Royal Sussex County Hospital. There was no trace of the case notes, but in the hospital register the cause of death is stated to be 'Cystic Disease of the Kidneys'.

Cases II. 1, 2, 3, 4, 5, and 6. These all died young, and no information is available as to the cause of death.

Case II. 7. Sarah A. Born 1853. Married. 2 children. Died at St. Thomas's Hospital, London, at the age of 57. Through the kindness of Dr. B. E.

Tompson, the Medical Registrar, I was allowed to see the case notes and the specimen of the kidney in the hospital museum.

Extract from case records (Dr. Hawkins):

'History. Eight weeks before admission the patient started to vomit; five weeks later she complained of pain in the abdomen with increasing constipation.

'Past illnesses. She is stated to have passed a renal calculus twenty-seven years ago, and one again since that time. She has suffered from "indigestion" for twenty years.

'Condition on admission. The patient lies exhausted in bed. The abdomen is distended, and a large mass, which is of a hard consistency, can be felt extending from the right hypochondrium downwards to the right iliac fossa. On the left side a similar tumour can be felt. The area of cardiac dullness is normal in extent, the apex beat being in the fourth space internal to the nipple-line. Signs of bronchitis are present in both lungs. Urine scanty; albumin +. The patient died two days after admission.

'*Post mortem.* Both kidneys are considerably enlarged and consist of a mass of cysts, some filled with serous fluid and others with opaque, chocolate-like material. Pelves not dilated. Very little normal renal tissue left. Weights: right 36 ounces, left 38 ounces. Liver normal with the exception of about six small cysts. Heart weighed 15 ounces.

Case II. 8. Alfred M. Born 1855. Age 74. Married. 5 children.

History. He had 'lumbago' for eighteen years in attacks lasting for a few weeks. More recently he has suffered from slight breathlessness on exertion. Sleep is good. There is no history of haematuria.

Examination. He appeared to be a healthy man looking not more than, say, sixty-five years. Examination of the abdomen showed in either loin the presence of an enlarged kidney, the surfaces of which were nodular. The lower pole of each kidney reached down to the level of the umbilicus. The liver was not felt. The heart's apex beat was in the fifth space in the nipple-line.

The sounds were normal with the exception of an accentuated aortic second. The blood-pressure was 190 mm. Hg (systolic) to 120 mm. Hg (diastolic). The fundus oculi showed slight thickening of the arteries and blurring of the disc edges. Both lungs were emphysematous. The urine was of a specific gravity 1008, and contained a trace of albumin, a few pus-cells, and an occasional red blood-cell. The blood contained 90 mg. of urea per 100 c.c. The urea concentration test was as follows:

	Percentage of urea.	Amount of urine. c.c.
Before urea	1·4	180
1 hour after	1·2	110
2 hours after	1·3	190

Case II. 9. Died young. No information available.

Case III. 1. William A. Born 1884. Age 45. Married. 2 children.

History. He has had two attacks of pain in the left hypochondrium twelve and sixteen years ago respectively. They lasted about twelve hours and were unaccompanied by vomiting. On each occasion he was confined to bed for a week. In addition, he has had what he calls 'lumbago'. There is no history of any urinary trouble.

Examination. In either loin could be felt a movable tumour. The one on the right side reached to about 1 in. below the umbilicus, whereas that on the left was slightly smaller. They were both nodular on the surface and moved with respiration. The liver was not enlarged. There was no evidence of cardiac enlargement. Blood-pressure was 150 mm. Hg (systolic). No abnormalities were discovered in the fundus oculi. The urine was of a specific gravity 1010, and contained a trace of albumin with a few epithelial and pus-cells. The

reaction was acid. Examination of the blood showed 20·8 mg. of urea per 100 c.c. The urea concentration test was as follows:

	Percentage of urea.	Amount of urine. c.c.
Before urea	1·9	85
1 hour after	2·0	104
2 hours after	2·3	87

Case III. 2. No trace.

Case III. 3. Charles M. Born 1881. Age 48. Single.

History. He was in the army for many years and during that time had two attacks of epididymitis. On questioning, he could remember no symptoms of renal pain. He had never had haematuria.

Examination. He was a healthy-looking man. No abnormality could be detected in the heart or lungs. The blood-pressure was 130 mm. Hg (systolic) to 90 mm. Hg (diastolic). The abdomen was normal in appearance, and neither kidneys, liver, nor spleen could be felt. Examination of the fundus oculi revealed no abnormality. The urine was of a specific gravity 1000 and acid in reaction. There was no albumin, sugar, nor abnormal deposits present. Examination of the blood showed 32 mg. of urea per 100 c.c. The urea concentration test was unfortunately unreliable owing to the fact that the patient had drunk a considerable quantity of beer before the examination. This fact may also account for the low specific gravity of the urine.

Case III. 4. Florence B. Born 1882. Aged 47. Married. 4 children.

History. She was examined by her family doctor in Australia, who stated that he was unable to discover any evidence of enlarged kidneys.

Case III. 5. Edith J. Born 1886. Age 43. Married. 4 children.

History. This patient was admitted to University College Hospital on August 26, 1927, complaining of pain in the left side of the abdomen, which had been present for fourteen days. It was accompanied by a feeling of faintness. She had had a previous attack some months before. The pain was described as a dull ache and was considerably relieved by resting in bed. There was no history of haematuria.

Examination. A hard, nodular swelling was palpable in each lumbar region in the position of the kidneys. These masses moved on respiration, and that on the left side could be displaced downwards to the level of the iliac spine. The heart was slightly enlarged and the impulse forcible. The blood-pressure was 150 mm. Hg (systolic) to 115 mm. Hg (diastolic). The fundus oculi showed no abnormality. The urine was of a specific gravity 1010, and contained a trace of albumin, a moderate amount of pus, and a few epithelial cells. Examination of the blood showed 39 mg. of urea per 100 c.c. The urea concentration test was as follows:

	Percentage of urea.	Amount of urine. c.c.
Before urea	1·1	12
1 hour after	1·3	73
2 hours after	1·3	54

Case III. 6. Alfred Edward M. Born 1887. Aged 42. Married. No children.

History. He stated that he had had an attack of severe abdominal pain associated with constipation three years previously. In addition he had occasional slight discomfort in the left loin. There was no history of haematuria. As a child he had scarlet fever.

Examination. He was a healthy-looking man. In the abdomen bilateral

nodular masses could be felt in the position of the kidneys, reaching down to the level of the umbilicus. They moved freely on respiration. There was no enlargement of the liver. The heart showed no abnormality, and the blood-pressure was 145 mm. Hg (systolic) to 100 mm. Hg (diastolic). The fundus oculi was normal. The urine was of a specific gravity 1010 and acid in reaction. There was a trace of albumin present with a few pus and epithelial cells. Examination of the blood showed 45 mg. of urea per 100 c.c. The urea concentration test was as follows:

	Percentage of urea.	Amount of urine.
		c.c.
Before urea	1·5	144
1 hour after	1·7	165
2 hours after	2·1	116

Case III. 7. Sydney M. Born 1889. Aged 40. Married. No children.

History. He suffered from attacks of constipation and loss of appetite with occasional vomiting for the last seven years. More recently he had shortness of breath associated with palpitation. He stated that he had become thinner. There was no history of haematuria. Eleven years ago a small tumour the size of a hen's egg was removed from the right knee at St. Bartholomew's Hospital.

Examination. The left kidney was considerably enlarged and nodular on the surface. The right was only just palpable beneath the lower border of an enlarged liver, which was apparently smooth on the surface, with the exception of a small nodule to the right of the midline. The cardiac impulse was forcible, but there was no increase in the area of cardiac dullness. The blood-pressure was 185 mm. Hg (systolic) to 120 mm. Hg (diastolic). No abnormalities were detected in the fundus oculi. The urine contained albumin and pus-cells. Examination of the blood showed 40 mg. of urea per 100 c.c. The Wassermann reaction was negative and the urea concentration test as follows:

	Percentage of urea.	Amount of urine.
		c.c.
Before urea	1·1	76
1 hour after	1·4	74
2 hours after	1·7	83

Case IV. 1. Irene A. Born 1913. Age 16. Single.

History. She has had no illnesses apart from an occasional cold.

Examination. She was a healthy-looking girl. Palpation of the abdomen showed the presence of a slightly enlarged right kidney, which appeared to be uneven on the surface. The left was just felt on deep inspiration. The liver was not enlarged. The heart was normal in every respect and the blood-pressure 100 mm. Hg (systolic). The fundus oculi showed no pathological changes. The urine was of a specific gravity 1010, and contained 0·075 per cent. of albumin and a few pus, but no red blood-cells. The urea concentration test was as follows:

	Percentage of urea.	Amount of urine.
		c.c.
Before urea	1·8	95
1 hour after	2·9	44
2 hours after	4·4	44

Case IV. 2. Aubrey A. Born 1917. Age 12. Single.

History. His mother stated that he got tired easily and suffered from constipation. There was no history of renal pain or haematuria.

Examination. He was a pale-looking boy. No abnormality could be detected in the chest or abdomen apart from a palpable sigmoid colon. Systolic

blood-pressure was 92 mm. Hg. The urine contained no albumin, blood, pus, or sugar. The urea concentration test was as follows:

	Percentage of urea.	Amount of urine.
		c.c.
Before urea	3·1	24
1 hour after	3·5	52
2 hours after	4·4	50

Cases IV. 3, 4, 5, and 6. These children, born in 1910, 1912, 1915, and 1917, and, aged 19, 17, 14, and 12 respectively, were living with their mother (Case III. 4), in Australia. The doctor reported no abnormal findings in any instance.

Case IV. 7. Ernest J. Born 1908. Age 21. Single.

History. No symptoms of any renal trouble could be discovered.

Examination. He was a slightly undersized boy. The abdomen was normal in all respects. There was no enlargement of the heart, and the blood-pressure was 135 mm. Hg (systolic) to 83 mm. Hg (diastolic). Retinoscopy showed the presence of well-marked myopic crescents in both eyes. The fundus was otherwise normal. His urine was of a specific gravity 1015, acid in reaction, and contained no abnormal deposits. Examination of the blood showed 33 mg. of urea per 100 c.c. The urea concentration test was as follows:

	Percentage of urea.	Amount of urine.
		c.c.
Before urea	2·4	40
1 hour after	2·2	110
2 hours after	2·8	64

Case IV. 8. Norman J. Born 1911. Age 18. Single.

History. The boy was stated by his father to be quite healthy, apart from two attacks of haematuria. The first occurred five years previously, and he was admitted to University College Hospital under the late Dr. Sydney Martin for investigation. The notes state that the boy had been taking part in some sports, and two days later it was noticed that he was passing a large amount of blood in the urine, which was partly clotted. This cleared up in three or four days. After admission to hospital, microscopic examination of the urine showed the presence of red blood-cells in a large quantity, but no casts. There was no rise in temperature. A radiogram of the renal tract showed no evidence of renal calculus. The second attack, which was similar in every respect to the first, occurred after a bicycle accident.

Examination. He was a slightly under-developed boy. The heart was not enlarged, and the blood-pressure was 105 mm. Hg (systolic) to 80 mm. Hg (diastolic). Both kidneys were palpable, but no definite irregularity of the surface could be detected. The urine contained 0·05 per cent. of albumin, a few pus-cells, but no casts or red blood-cells. Examination of the blood showed 13·6 mg. of urea per 100 c.c. The urea concentration test was as follows:

	Percentage of urea.	Amount of urine.
		c.c.
Before urea	2·6	22
1 hour after	2·9	40
2 hours after	3·4	33

Cases IV. 9 and 10. Joan J. and Betty J. Aged 14 and 11. Born 1915 and 1918 respectively. They were both healthy-looking girls; no abnormalities could be detected in either case.

Below are set out the salient features of the affected members in tabular form:

No.	Age.	Sex.	Kidneys.*	Urine.				Urea conc. test.	Blood-urea.†	Blood-pressure.	
				S.G.	Albumen.	R.B.Cs.	Pus.			S.	D.
I. 1	53	F	...	...	...	...	...	...	...	...	...
II. 7	57	F	+++	...	+	...	...	...	...	...	...
II. 8	73	M	++	1008	trace	+	+	poor	90	190	120
III. 1	45	M	++	1010	trace	0	+	fair	20·8	150	...
III. 5	43	F	++	1010	+	0	++	bad	39	150	115
III. 6	42	M	++	1010	trace	0	+	fair	45	145	100
III. 7	40	M	++	...	+	0	+	bad	40	185	120
IV. 1	16	F	+	1010	+	0	+	good	...	100	...
IV. 8	18	M	?+	...	+	0	+	good	13·5	105	80

* +++ = gross enlargement.
++ = considerable enlargement.
+ = moderate enlargement.

† These figures are in terms of milligrams per 100 c.c. of blood.

... = no observation.

In further explanation of the renal tests employed, it should be stated that the urea concentration test was done in the manner described by Maclean. The blood-urea was estimated by the hypobromite method.

The blood-pressures were all recorded by the auscultatory method, with the patient lying on a couch, the head being slightly raised. The instrument used was the mercury sphygmomanometer.

Discussion.

One of the most striking points emphasized by this series is the remarkable absence of symptoms in individuals whose kidneys are severely damaged. That there is a definite decrease of renal efficiency with increasing age is demonstrated by the results of the urea concentration tests. In the first and second generations the evidence is insufficient, but the third, which is composed of individuals in the fifth decade, shows as a whole a significant impairment of renal function. This is in marked contrast to the two early cases in the fourth generation. The blood-urea would seem to be a less sensitive index.

The urine of the affected members shows fairly constant alterations. Although haematuria is a not infrequent sign of the abnormality, red blood-cells were present in only one case. Albumin, on the other hand, was a constant finding, although never in large amount. The other interesting fact is the frequency with which pus-cells were found. These again were only in small quantity, with the exception of Case III. 5, who had a definite pyelitis at the time she was in the Hospital.

The apparent effect on the cardio-vascular system is interesting. In the one case in the second generation whom I examined, the blood-pressure was high and there was evidence of changes in the retinal blood-vessels, but owing to the age of the patient (74), it would be unwise to draw any definite conclusions. In the

instance of III. 7, the case is different, for here is a man aged 40, who has no evidence of any renal lesion apart from the one under discussion, with a blood-pressure of 185 mm. Hg, and symptoms indicative of a poor exercise tolerance. That his kidneys are badly damaged is shown by the inefficient manner in which urea is excreted by them.

The other members of that generation all tend to show a blood-pressure which is slightly higher than is normal.

Turning to the familial aspect of the series, it is shown that there is no break in the transmission of the abnormality from parent to child, and the fact that it can be transmitted either through the male or female is well demonstrated.

The family is not one that is rapidly increasing in numbers, and in that respect differs from the 'East London Family' reported by Cairns. Nevertheless, I think that too much stress should not be laid on this point, as the members were apparently of a higher social standing and therefore more likely to limit the number of their children.

In conclusion I should like to express my thanks to Dr. Bolton for allowing me to publish the original case, III. 5, of this series, and to Miss Janet Vaughan for the assistance in carrying out the pathological tests.

REFERENCE.

1. Cairns, H. W. B., *Quart. Journ. Med.*, Oxford, 1924-25, xviii. 359.

VARIATION OF FREE HYDROCHLORIC ACID AND TOTAL CHLORIDE IN THE UPPER AND LOWER PARTS OF THE STOMACH [1]

By ROBERT J. DUTHIE

(From the Royal Infirmary, Aberdeen, and the Tor-na-Dee Sanatorium)

With Plate 33

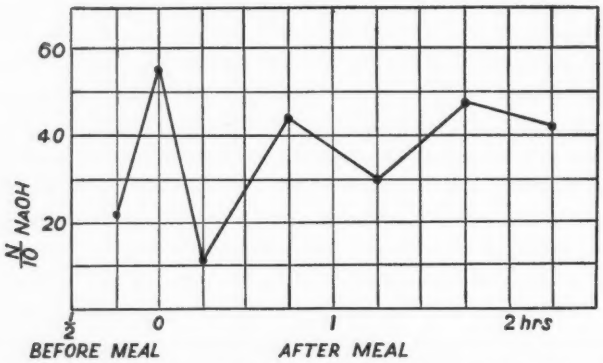
This investigation was undertaken to obtain further information regarding the concentrations of free hydrochloric acid and total chloride in the gastric contents, and follows a preliminary note (1) in this journal. Double fractional test-meals have been made on twenty-five patients with two small-bore tubes sutured together, one for obtaining samples of the contents from the cardiac, the other from the pyloric part of the stomach, as described in the preliminary note. The distance between the openings of the tubes in the cases described in the present communication is five inches, not eight as noted previously.

The first point of importance demonstrated during the investigation was that only by radiological examination could the exact position of the tubes be determined. The marks on the ordinary fractional test-meal tube may be useful in indicating how much tube is swallowed, but are misleading in determining the position of the tube in the stomach. The latter point is very important in assessing the value of the results of a fractional test-meal. The end of the tube may be in the duodenum, as in the case illustrated in Pl. 33, Fig. 1. The specimens from the duodenal tube in this instance contained free hydrochloric acid, and there was nothing suggesting that the stomach was not the origin of the specimens, except, perhaps, the fact that bile was present; the latter, however, is frequently found in the stomach and is due to regurgitation. In several experimental cases, specimens without free hydrochloric acid were obtained from the duodenum—some of them not containing bile—and, but for radiological examination demonstrating that the tube was in the duodenum, and the fact that large quantities of acid were obtained through a shorter tube in the stomach, these cases might have been classified as having no free acid in the stomach. Another incident which may upset the result of a test-meal is illustrated in Pl. 33, Fig. 2, which shows the tube twisted in the stomach. Specimens thus obtained may come from the cardiac part of the stomach, and, as will be shown later, are often of lower acidity than those from the pyloric part, and a false result may be obtained. Further, the end of the tube may rise above the fluid level

[1] Received February 18, 1929.

in the stomach, and when air is aspirated one is apt to conclude that the stomach is empty. These two examples show the necessity for at least screening the patient during a test-meal to determine the exact position of the tube. The above findings suggest, in addition, that former statistics regarding fractional test-meals are not correct, unless the position of the stomach tube has been accurately determined, and that some cases with normal acidity have been tabulated as having no acidity because the supposed gastric specimens came from the duodenum. Successive test-meals in cases where the pharmacological action of drugs has been determined must also be considered with reservation, unless the stomach tube has been proved to have been in identical position on each successive occasion.

Free Hydrochloric Acid in the Upper and Lower Parts of the Stomach.



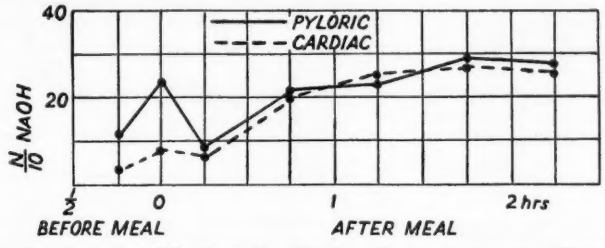
GRAPH A. Greatest differences in free hydrochloric acid noted in a series of 25 test-meals with double stomach tube (normal and abnormal cases).

Note.—Specimen of fasting gastric contents removed a quarter of an hour before meal, and another immediately before meal. Total fasting contents not removed.

Graph A indicates the greatest differences of free hydrochloric acid observed in the series of test-meals during the respective periods of aspiration. The differences are plotted in the usual terms of NaOH N/10. The greatest difference is fifty-five units, noted a quarter of an hour after the tube had been passed, that is immediately before the test-meal was given. In this particular case the pyloric secretion was of higher acid concentration than the cardiac. The lowest reading of maximum difference is a quarter of an hour after the test-meal. This is not unexpected, as these are the first specimens examined after dilution by the test gruel. Moderately high readings of difference are noted three-quarters of an hour and 2¼ hours after the meal.

Graph B indicates the average acidity of the pyloric and cardiac parts of the stomach when the test-meals are taken collectively. It will be seen that, immediately the tubes are passed, the pyloric region has an average of 7·5 units higher than the cardiac region, and when the tubes are left *in situ* for a quarter

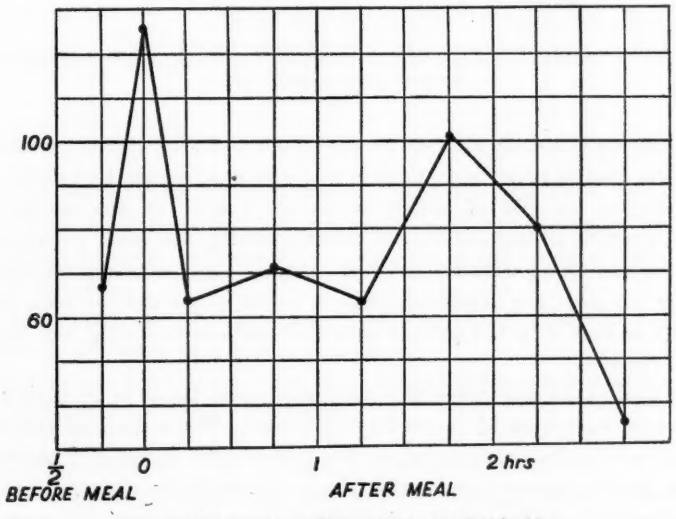
of an hour before the meal, there is an average rise of acidity in both parts, but a more rapid rise in the pyloric. After the meal there is a dilution of acidity in both parts, and the average difference is small. There is, however, a preponderance of acidity in the pyloric part. The only period where the cardiac secretion exceeds the pyloric is at 1¼ hours after the test-meal, and even then the difference is small.



GRAPH B. Average acidity in series of test-meals at pyloric and cardiac regions respectively.

These two graphs suggest that, if successive test-meals were done on each case and the results averaged, a better idea of the acidity of the stomach contents would be obtained. The results, however, would not be worth the labour entailed.

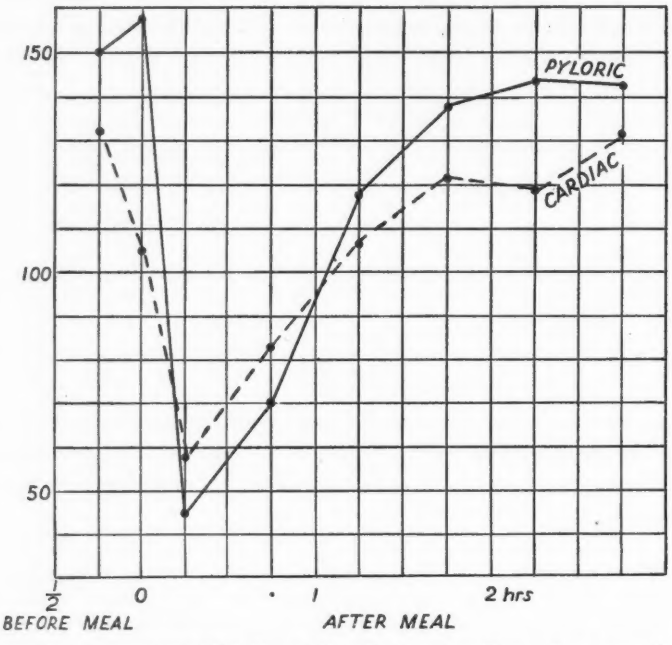
Total Chloride in the Upper and Lower Parts of the Stomach.



GRAPH C. Greatest differences in total chloride.

The total chloride content of the stomach is always much higher than the acidity, and there are, as one would expect, greater differences in concentration in the upper and lower parts.

Graph C indicates the highest differences noted in the total chloride, and Graph D shows the relation of the average readings from the cardiac and pyloric regions.



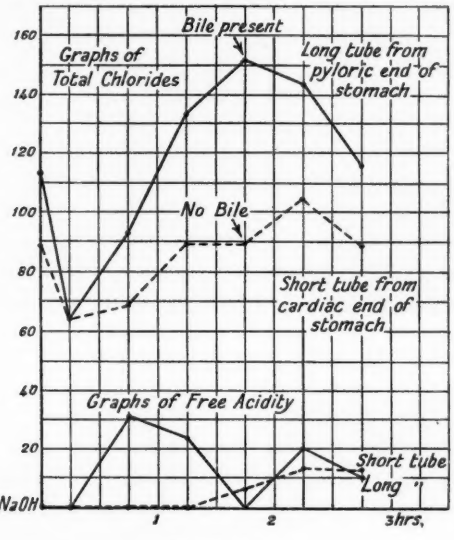
GRAPH D. Average total chloride, at the pyloric and cardiac regions respectively, in same series of test-meals.

Comparing Graph D with the similar graph of acidity (B), one notices that, for the first quarter of an hour, there is a rise of chloride at the pyloric region, very similar to the rise of acidity previously noted. In the cardiac region, however, there is a decrease in the chloride during the same period—not an increase as was found with the acidity. During the first three-quarters of an hour after the meal, the average chloride is higher in the cardiac part, but after an hour it is higher in the pyloric part, and remains so during the remaining period of the test.

The acidity, as was previously mentioned, also tends to be higher at the pyloric part, except at 1¼ hours after the meal. These findings suggest that the increase of chloride occurring at the pyloric part is not due to regurgitation from the duodenum, because, if this were the cause, simultaneous neutralization or lowering of the acidity would also be expected at this area. It is likely, however, that the relatively low chloride and acidity at the cardiac part is due mainly to dilution by saliva which would lower both concentrations at the upper part of the stomach. Although the patients, on whom the above tests were made, were carefully instructed to expectorate all saliva, yet, I believe,

a considerable quantity finds its way along the tubes to the cardiac region of the stomach.

Occasionally, it may be mentioned, there occurs a sudden increase of chlorides (noticed also by several other observers) in the pyloric region, accompanied by bile and a reduction of acidity. This sudden increase in the total chloride cannot be due to the neutralization of acids alone, but must be due to regurgitation of fluid from the duodenum containing a higher total chloride concentration than the gastric secretion. Graph E illustrates a case in point.



GRAPH E.

Summary.

The variation of free hydrochloric acid and total chloride in the upper and lower parts of the stomach has been examined in twenty-five cases.

The importance of determining the position of the stomach tube by radiography is noted.

Free hydrochloric acid and total chloride are generally in higher concentration in the lower part of the stomach.

The higher total chloride in the lower part of the stomach is not, as a rule, due to regurgitation from the duodenum.

My thanks are due to Dr. William F. Croll for facilities afforded me in his wards at the Aberdeen Royal Infirmary, and to Dr. J. M. Johnston for facilities in the Tor-na-Dee Sanatorium. I wish to acknowledge much help from the radiological departments of both institutions.

REFERENCE.

1. Duthie, R. J., *Quart. Journ. Med.*, Oxford, 1926–27, xx. 265.



FIG. 1. Long tube in duodenum, the short in stomach



FIG. 2. Tubes twisted in stomach

ACIDAEMIA AND ALKALAEMIA IN THE DIARRHOEA AND VOMITING OF INFANTS[1]

By MONTAGUE MAIZELS and CATHERINE B. McARTHUR
(From The Department of Pathology, The Infants Hospital, Westminster)

Introduction.

During the summer of 1928 cases of acute gastro-enteritis were admitted to the wards of the hospital; the numbers growing and the severity increasing week by week.

It is well known that acidosis and anhydraemia occur in such cases as these, and in their treatment the giving of alkali usually occupies an important place. It was thought worth while, therefore, to determine before the commencement of treatment the degree of acidosis present, and its response to the administration of sodium bicarbonate. To this end, the pH and bicarbonate content of the plasma were measured. In many of the cases, too, the chloride content was estimated and, in some of them, the urea and phosphate content also.

It was further thought desirable to find out if the presence or absence of acidosis could be inferred from the examination of the urine by simple and familiar methods. Accordingly, the pH of the urine, the titratable acidity, the ammonia-combined acid and urea were estimated by methods which, if not highly accurate, were at least easy and quick. The presence or absence of acetone bodies was also determined, and the content of chloride and phosphate.

Methods.

The blood required for examination was obtained from the heel, great toe, or thumb, by puncture with a Hagedorn needle. In all but severe cases the extremities were usually warm, and about 0·4 c.c. of blood was obtained with only light pressure. The blood was allowed to flow under paraffin in a tube of the type described by Martin and Lepper (1). At first, potassium oxalate was used to prevent clotting, but later heparin was preferred, so that the haemolysis sometimes seen with oxalate might be avoided. In severe cases of diarrhoea the foot, if cold, was placed in warm water for some minutes and dried with a hot towel. Even so, the flow might be sluggish, and where this was the case the possibility of error arose from two sources.

Of the errors arising from the method of collection, there is first the effect of tissue stasis. Peters, Bulger, Eisemann, and Lee (2) have shown that stasis causes water to flow from the blood to the tissues, raises the acid content, and

[1] Received February 22, 1929.

lowers the chloride of plasma. The acids are carbon dioxide and organic acids resulting from imperfect oxidation. Even after severe stasis, however, the effects on the plasma bicarbonate and chlorides are relatively slight. The most marked alteration recorded by Peters and his co-workers is a change in the CO_2 from 60·8 to 65·4 volumes per cent., of the chloride from 0·370 to 0·349 per cent., and a fall in pH from 7·34 to 7·29. In other cases, a slight fall of CO_2 has been noted. It follows that the striking changes found in capillary blood in cases of infantile diarrhoea are in the main, due to causes other than local stasis. In other words, the immediate effects on the blood of local stasis in the part from which blood is drawn, though definite, are relatively insignificant when compared with the great change wrought by disease. This does not mean that even slight stasis in the vascular system as a whole cannot cause profound alterations in the blood. It merely implies that if the blood as a whole is normal, then stasis in the foot will not cause much change in the capillary blood flowing from the heel; while if, on the other hand, the blood be modified by some general disorder, then local stasis will not mask the abnormality.

A second error arises from the loss of CO_2 which occurs during the process of collection. When the blood flow is rapid this is negligible; but when it is extremely slow, loss of carbon dioxide from the blood as it flows in a thin stream down the side of the collecting tube must be considered. Whereas stasis in the tissues before collection tends to lower the alkali reserve of the plasma and lower the chloride content, loss of CO_2 after collection would lower the bicarbonate content but raise the chloride. Actually, the loss of CO_2 was much less than might have been expected. Thus when the blood was allowed to flow down the collecting tube excessively slowly, the fall in bicarbonate content was only 7 per cent., and even when the collected blood was run up and down the side of the tube again and again, only part of the CO_2 had escaped, with a lowering of the bicarbonate content of less than 13 per cent.

These findings are illustrated in the following table:

TABLE I.

Exp.	Remarks.	Plasma Bicarb. (molar).	Plasma NaCl. %
1	No stasis; rapid flow	0·030	0·57
	,, ,, slow ,,	0·0288	0·59
	Stasis; slow flow	0·028	0·57
2	No stasis; rapid flow	0·0262	0·63
	Stasis; slow flow	0·0258	0·62
3	No stasis; rapid flow	0·0306	0·60
	,, ,, slow ,,	0·0263	0·60
	Stasis; slow flow	0·0267	0·55

It will be seen, therefore, that errors arising from local stasis or loss of CO_2 after collection are only slight in cases of average severity, and even in the worst cases the variations in plasma bicarbonate and chloride were so marked as to make one content that the results obtained were a proper index of changes occurring in the general circulation during life. In support of this it may be

noted that in three cases of extreme dehydration with peripheral stasis, where acidaemia might have been expected, a condition of alkalaemia was found. (Table IV, Cases 5, 8, and 9.)

Regarding the collection of urine; no attempt was made to secure twenty-four hour specimens; in female infants with diarrhoea, one is fortunate to obtain even one uncontaminated specimen in the day. In male infants, on the other hand, it is easily possible to obtain a satisfactory specimen, but the attachment of the necessary test-tube for long periods seemed to cause a good deal of unrest.

In any case, if the blood changes are to be correlated with the urine, a single specimen collected at about the time of blood examination is of more value than a representative daily specimen. For this reason the blood examination was carried out within an hour or two of the urine being obtained, and usually some time before midday. It was not, of course, always possible to restrict blood examinations to the morning, and, under these circumstances, additional specimens of urine were obtained. As soon as the urine was passed it was covered with toluol and examined as quickly as possible.

Chemical methods. The investigation of the blood was greatly hampered by the difficulty in obtaining sufficient material, and by the necessity of limiting the amount withdrawn so that a series of observations might be made without detriment to the patient.

1. pH was ascertained by Martin and Lepper's method (3). The readings were taken at room temperature. How far the temperature correction given for adult blood is applicable to infants, and especially to those with marked disturbances of salt and protein concentration in the blood, is doubtful, and requires investigation. It is assumed for the present that the pH values obtained are a fair indication of whether the blood is more alkaline or more acid than normal. It is, however, unfortunate that one could not obtain enough blood to supply additional data for the calculation of pH from the Hasselbalch equation.

2. Plasma bicarbonate was determined by the method of Van Slyke, Stillman, and Cullen, modified by Payne (4). The titration was performed with a micrometer syringe and the error for 0·1 c.c. of plasma was less than 5 per cent.

3. Plasma chloride (as NaCl) by Claudius's method (5). We have sometimes been compelled to carry out this examination on 0·05 c.c. of plasma. Under these circumstances, results may differ by $\pm$ 5 per cent.

4. Urea, by Twort and Archer's method (6).

6. Phosphate, by Briggs's method (7).

Urine examination. 1. pH by comparison with standard indicators. Values greater than 7·5 are probably due to loss of CO_2 on standing.

2. The titratable and ammonia-combined acid were determined respectively, before and after the addition of formalin, with N/50 NaOH. pH 7·2 was taken as the end point in all the titrations recorded in this communication, but recently it has been thought better to titrate to a higher pH with phenolphthalein as an indicator.

3. Urea was estimated by the hypobromite method. The ammonia coefficient referred to in the text is the ratio of ammonia nitrogen to urea nitrogen. The hypobromite method is open to many criticisms, but the results obtained by it in the different specimens of normal and abnormal urines are comparable.

4. Phosphate, by Briggs's method.

6. Chloride, by Volhard's method.

Results in normals. Blood. pH. Fifteen determinations (corrected to 37° C.) varied between 7·31 and 7·42. Eleven of these lay between 7·36 and 7·42.

Plasma bicarbonate. Twenty-two out of thirty cases had figures between 0·023 and 0·028 molar. One case gave a result of 0·03 M.; the two lowest results were 0·019 and 0·0195 M. We are inclined to think that the lower results—below 0·023 M.—are associated with the presence of minor ailments—teething or feeding difficulties.

Plasma chloride (as NaCl) varied between 0·56 and 0·64 per cent.

Urine. pH. Thirty-one out of thirty-seven specimens were more alkaline than pH 5·5, and of these, seventeen were more alkaline than pH 6·5. The pH of the most acid urine was 5·3.

Ratio of titratable to ammonia-combined acid. Where the numerator is small this fraction tends to become rather inaccurate. Therefore, in the following generalization, very dilute urines (with a urea content of less than 0·75 per cent.), or urines near neutrality (pH greater than 6·5) have been excluded; in the urine of normal infants, the ratio of titratable to ammonia-combined acid lies between 1/1 and 1/2. (Fifteen out of nineteen specimens.)

Ammonia coefficient. Thirty-eight determinations were made by the method referred to previously. In only four of these was the coefficient greater than 7 per cent. The highest figure was 11 per cent.

Chlorides were present in all urines in fair quantity, the amount varying with the dilution. The amount was over 0·06 per cent. in thirty-four of thirty-seven cases, and over 0·1 per cent. in twenty-five cases.

Phosphates, expressed as P_2O_5. Usually below 0·3 per cent. (Eighteen of twenty cases.) The phosphate content was less than would have been expected from the acid titration.

Most of the urines referred to above were collected in the morning. A few, however, were passed later in the day, and in view of the alterations in the urine brought about by the digestive processes and by sleep, it may be asked if these variations were capable of masking the changes due to acidosis. The examination of numerous normal and abnormal urines has shown that individual specimens passed during the day differ among themselves in several respects, and especially in the reaction and titratable acid. If, however, the proviso with regard to dilution and reaction be accepted, then it may be said that the ammonia coefficient and ratio of titratable to ammonia-combined acid are fairly comparable, and if one specimen of urine shows an abnormality, then all the others will, provided that the condition of the blood does not alter much in the meantime.

Cases of Diarrhoea and Vomiting.

Only cases of moderate or marked severity were selected for study. Of these forty-eight cases, treated and untreated, twenty-eight showed acidosis (with a plasma bicarbonate of less than 0·02 molar), and twenty, alkalosis (with a plasma bicarbonate of more than 0·028 molar). In ten of the twenty cases the alkalosis was associated with the excretion of an acid urine.

Group I. Cases with acidosis. (Table II.) Many of these cases of acute gastro-enteritis with acidosis were typically dehydrated. The eyes were sunken, the fontanelle depressed, and the extremities colder than normal. The lips and tongue were dry and strawberry red in colour, while the skin was inelastic, thrown into folds, and sometimes slaty coloured. In other cases this colouration, the result of cyanosis, was absent.

Post-mortem examinations were performed on nine of the cases in Table II, and in two other cases. All showed marked fatty changes in the liver. The kidneys were also somewhat fatty; especially in Cases 16, 24, and 25. The lungs were normal in half the cases. Oedema, hypostatic congestion, or definite consolidation were present in the others. Inflammation of the mucosa of the ileum was present in all cases; in only two of these were the Peyer's patches specially involved. The lesion varied from slight injection to severe inflammation with superficial necrosis. The colon was also involved, but not so severely as the small intestine. The stomach usually looked normal, or slightly pinker than normal, and, occasionally, submucous haemorrhages were found (16, 22). The pia-arachnoid was oedematous and the grey matter hyperaemic in four cases (including Nos. 8, 20, 22). Oedema was present alone in two cases. In one of these, No. 16, the hyperaemia was very intense and small haemorrhages were present on the convexity of the brain. Doubtless these cerebral changes account for the head retraction and the meningeal cry so commonly noted in cases of acute summer diarrhoea.

The chemical findings in cases of diarrhoea with acidosis are summarized in Table II. The last three columns of this table indicate the doses of drugs that have been administered. Alkali was given in combination with salt and glucose in the following proportions: sodium bicarbonate 0·5 per cent., sodium chloride 0·45 per cent., and glucose 2·5 per cent. The solution was sterilized by boiling and the final pH varied from 8·6 to 9·2. The ordinary numerals in these columns give the doses of bicarbonate in grains. The actual figures recorded stand for the amount of alkali administered before and up to the time of the investigations recorded in the same line. If, for example, the figure were 30, then 30 grains were given in the twenty-four before the record; if it were 30/3, then this amount was given in the three preceding days. The latter method of notation was only adopted when the distribution of bicarbonate over a number of days was fairly even. It follows from the glucose saline bicarbonate preparation used that the amounts of sodium bicarbonate and sodium chloride given were roughly equal. The roman numerals found in the last three columns

indicate the amount of ammonium bromide given as a sedative, and the roman figures in square brackets stand for the doses of ammonium chloride given with the object of combating alkalosis.

In the cases of diarrhoea with acidosis the pH was almost always slightly reduced—the average figure was 7·24, and the lowest figure recorded was 7·14, corresponding to a plasma bicarbonate of 0·0035 (Case 17). The reduction of plasma bicarbonate was often extreme. In Cases 1, 2, 3, 9, 12, 15, 16, 17, 20, 25 it was below 0·01 molar. If the pH and plasma bicarbonate values are compared however, it will be seen that the acidosis is compensated to a considerable extent. Hence it follows that the pH is a less sensitive index of the necessity for alkali treatment than is the plasma bicarbonate.

The prognosis did not seem to depend on the initial blood bicarbonate; in some fatal cases the reserve was only moderately depleted, while in others that recovered it was, at the outset, very low indeed. The failure of response to alkali treatment was a better index of severity; cases not responding did badly (3, 4, 5, 6, 7, 14, 19, 22, 24, 25). On the other hand, of those that reacted to treatment, some did well (2, 15, 17, 21, 26); others did badly (1, 8, 16, 23, 25).

There are not enough figures for plasma chlorides to allow of conclusions being drawn. They were high in Cases 16 and 19, within normal limits in Cases 15, 18, 21, 26, and 27, and low in Cases 17, 20, and 22. Of the last three cases, only 22 had received treatment before blood examination. In view of the common statement that plasma chlorides are raised in acute summer diarrhoea with acidosis and anhydraemia, the striking reduction of chloride in three cases recorded above is of interest.

The urea content of the blood was also only estimated in a few cases. It was raised in eight of eleven determinations, and was over ten times normal on three occasions.

The urine was always acid and usually contained amorphous urates; nevertheless, even in severe acidosis the reaction of the urine was seldom more acid than pH 5·5 (six of twenty determinations). On the other hand, the highest pH recorded was 6·3. It appears that if the pH of the urine is more than 6·5, acidosis is probably absent. It is curious that although the kidney is able to excrete a urine far more acid than pH 6·0, the pH of the specimens was in the neighbourhood of this moderate figure in no less than fourteen of twenty records. When the blood became more alkaline than normal, the pH of the urine usually rose above 7·0.

Acetone bodies were present in only five of seventeen specimens of urine which were passed at a time when acidosis was known to be present. Usually not more than a trace was found.

In eighteen of twenty-one specimens the ammonia-combined acid was more than 2·5 times as great as the titratable acid (that is the ratio was less than 1/2·5) and on the average it was about five times as great. It is important to note, however, that in some severe cases of acidaemia the ratio was quite large. Thus, in seven selected cases, where the plasma bicarbonate averaged 0·011 molar,

the average ratio was 1/2·5. In other cases, where the bicarbonate reserve was normal, the ratio was represented by quite a small fraction; but here the urines were either very dilute or nearly neutral.

The magnitude of the ammonia coefficient was not proportional to the degree of acidosis, for although it was above 8 per cent. even in the presence of slight acidosis, and was above 20 per cent. in certain severe cases, in other cases of extreme acidaemia it was only slightly over 10 per cent. The lowest figure recorded in seventeen observations was 8·9 per cent. On the other hand, in some cases when the plasma bicarbonate became normal as a result of treatment, or for some other reason, the ammonia coefficient remained above 8 per cent. for several days. (Cases 2, 3, 6, 15, 17, 21, and 26.) In Case 17, where alkalaemia was present the urine was alkaline (pH 7·4) but the ammonia coefficient was over 20 per cent. It is difficult to understand why the kidneys should continue to excrete such large quantities of ammonia in the urine under these circumstances, when there is already an excess of fixed base in the blood.

One may conclude, therefore, that if the ammonia coefficient is below 8 per cent., acidosis is absent, but if it be above 8 per cent., no deductions can be made as to the condition of the blood.

It will be seen that the information that can be derived from the urine concerning the blood is in the nature of negative evidence: if the urine is alkaline, or the acid ratio is more than 1/2, or the ammonia coefficient is less than 8 per cent., acidosis is probably absent. But even in the presence of alkalaemia the urine may be acid, the acid ratio may be less than 1/2, and the ammonia ratio may be above 8 per cent.

The urinary chlorides were very low—below 0·06 per cent.—in five of nine observations made when acidosis was present. Three of these observations are of special interest:

Case 15: here, on September 26, a temporary alkalosis and low plasma chloride were associated with oedema. Next day, the alkalosis had increased and the chloride had fallen still farther, while the oedema became more marked. Two days later the blood was found to be normal, and the oedema had disappeared.

Cases 16 and 21 are of interest because they show very little chloride in urines of high concentration, although the plasma chloride was raised. Both these cases were dehydrated, and the bicarbonate reserve was reduced.

In contrast to the chlorides, the few phosphate records available were not low. In Cases 21 and 22 they were particularly high.

The response to alkali treatment was naturally obscured by the tendency to spontaneous improvement in some cases. Roughly speaking, a drachm of bicarbonate a day for one or two days would raise the plasma bicarbonate by 0·015 molar, in infants averaging 8 lb. in weight, where the initial figure had been below 0·02 molar. When it was above this figure similar doses appeared to cause less alteration. Smaller amounts of bicarbonate, even if continued for several days, were much less efficacious—particularly in the more severe cases. In the latter the results were particularly uncertain. In some cases, 45 grains

daily for several days failed to produce any rise in the plasma bicarbonate, while in other cases, even larger doses than this were unable to prevent a fall; such cases were Nos. 1 (29th 3), 3 (17th 5), 4 (11th 6), 9 (5th 7), 17 (10th 10), 22 (7th 11), and 24 (17th 8).

Ammonium bromide was sometimes given in cases of restlessness and there was no evidence that it caused any ill effects; sodium bicarbonate, of course, was being given at the same time.

Although subcutaneous and rectal glucose-bicarbonate-salines were useful from the point of view of supplying extra fluid, their effects on the plasma bicarbonate did not indicate that they were specially able to alter the reaction of the blood. It seems that the larger oral doses, though their absorption be uncertain, are more effective therapeutically than the very much smaller amounts that can be given by other routes; although the latter attain special importance where the patient is not 'taking well'. We have had no experience of the administration of intraperitoneal fluid, other than normal saline.

It cannot be said that the relief of the acidaemia results in recovery; in some cases the inflammatory process may cease before the acidaemia and then the relief of the latter may avert a fatal issue. But in other cases, where diarrhoea and vomiting have existed for several days, severe toxaemia on the one hand, and progressive disturbance of salt balance on the other, make the treatment of the acidaemia as ineffectual in this condition as it is in chronic nephritis.

Group 2. Cases with alkalaemia and acid urines. Table III. This group of cases is characterized by the presence of a raised pH and bicarbonate in the blood, together with the secretion of an acid urine.

Clinically, there is nothing distinctive; dehydration may be severe, but is usually slight or moderate. Cyanosis is absent, although marked pallor without anaemia is common. Respiration is usually normal, and the extremities are warm. A watery appearance of the conjunctivae is often noticed. Nervous symptoms are common; rigidity, athetosis, tremors, and even fits may occur. These are doubtless of cerebral origin, yet the attitude of limb often found, and the presence of muscular twitching, suggest the possibility of co-existing tetany.

Concerning the post-mortem findings Case 1 showed a fatty liver and extreme dilatation of the colon; otherwise there was no abnormality. Case 6 had a fatty liver and marked congestion of the colon and ileum. Case 8 showed hypostatic congestion of the lungs and a slightly fatty liver. The ileum was congested, but the colon was especially inflamed, with numerous ulcers extending through the mucous coat. There was a slight excess of fluid in the pia and the grey matter was very congested; over the ventral surface of the medulla there was a small haemorrhage. Case 9 had multiple pyaemic abscesses in the lung. The liver and kidneys were fatty. The gut was inflamed; especially the colon. Double otitis media was present. The pia-arachnoid was oedematous and the grey matter was pinker than normal.

It will be seen that there is nothing characteristic about the findings, except that the colon was specially involved; being extremely dilated in the first case and unusually inflamed in the others.

As regards chemical findings, the plasma bicarbonate was raised in the group of cases now under discussion. In Cases 3, 4, and 9 it was high prior to the administration of alkali; while in Case 5 very little treatment had been given. Further, the administration of alkali by mouth resulted in an extraordinary accumulation of bicarbonate in the blood, with little or no change in the reaction of the urine. The highest figure reached was 0·058 molar. This anomalous condition persisted for several days. In Case 8 the alkalosis was present from October 1 until October 22, although alkali treatment was stopped on October 3. The pH of the blood in these cases was raised, but not to the level that one might have expected from the bicarbonate reserve. Doubtless the presence of pulmonary lesions in Cases 8 and 9 contributed to the partial compensation of the alkalosis.

The plasma chlorides were nearly always low; frequently below 0·5 per cent. The lowest figure reached was 0·34 per cent. in Case 9. In general, it will be noted that the chloride varies inversely as the bicarbonate.

The blood urea was raised in two cases with severe toxaemia. In three others, one of which, Case 8, was of a severe type, the urea was not raised—in spite of the fact that the bicarbonate in the blood was high. (See Case 8, November 12.)

The pH of the urine was usually less than 6; seventeen of forty-three specimens were more acid than pH 5·6, and numerous examples of exceptional acidity were encountered. This contrasts with the findings in diarrhoea with acidaemia, where the reaction of the urine was usually in the neighbourhood of pH 6, and extreme acidity was rare. Amorphous urates were usually present, and acetone bodies were usually absent.

The ammonia-combined acid was more than 2·5 times as great as the titratable acid in only four of twenty-eight urines passed at a time when alkalaemia was present. In nine cases the titratable acid exceeded the ammonia-combined acid; an unusual finding, which, however, has been recorded in certain cases of nephritis. (Henderson and Palmer (8).) The ammonia coefficient was very variable; in some cases of alkalaemia it was high, but as a rule it was below 10 per cent.

The chlorides in the urine were always very low and frequently were absent altogether. The phosphates on the other hand were high—over 0·4 per cent. in fourteen of twenty-five specimens. The highest figure attained was 1·46 per cent.

Extra sodium chloride caused some improvement in these cases, but in the face of persistent diarrhoea the improvement was not maintained.

Group III. Various cases. (*Table IV.*) Table IV shows several cases of interest which cannot be placed in either of the two preceding groups, either because the chemical findings are not appropriate, or because they have been modified by much treatment.

Case 1 shows the effects of the administration of excessive amounts of sodium chloride; the plasma chloride is very high, and, probably as a result, the plasma bicarbonate is low.

Cases 2 and 3 have no deficiency in plasma bicarbonate, but the effects of the diarrhoea are shown in the reduction of chloride.

Numbers 4, 5, 6, 7, and 8 were all cases of alkalaemia, 4 and 6 had received no previous treatment with alkali and presumably represent a real primary alkalaemia, in which the loss of acid has exceeded the loss of base. Case 5 was admitted with severe anhydraemia, the presence of which was confirmed by blood count: red cells 6,400,000 per cubic millimetre. A condition of acidosis was expected, but the urine was alkaline and the alkali reserve of the blood was raised. Marked alkalaemia was found in Cases 6 and 7. In these the plasma chloride was low and the urine was alkaline. Yet although the blood chloride was low, the urinary chlorides were quite high—especially in No. 6, where the urea was only 0·5 per cent., while the chloride was 0·3 per cent.

Cases 9 and 10 showed a moderate alkalaemia after moderate dosing with alkali. In Case 9 the administration of alkali was stopped but the alkalaemia persisted; three grains of ammonium chloride were given on the night of the 19th, and by the morning of the 20th the plasma bicarbonate had fallen from 0·033 to 0·0135 molar. This is an example of a profound fall in the alkali reserve of the blood after an apparently insignificant dose of ammonium chloride.

Discussion.

There has been considerable discussion concerning the causes of acidaemia in diarrhoea and vomiting. It is generally agreed that acetone bodies do not account for the acidaemia, for they are generally absent or present only in small quantities in the blood and urine. This agrees with the observations in the present paper where their presence was only occasionally observed, while they were absent in some of the very worst cases.

Marriott (9) ascribes the acidaemia to anhydraemia. First, deficient circulation through the kidneys leads to imperfect renal excretion with phosphate retention and an acidaemia of the type occurring in nephritis. Marriott points out, however, that although the inorganic phosphate in the blood was high, this alone would not account for the reduction of bicarbonate observed in his cases. Secondly, anhydraemia is followed by peripheral stasis, and this in turn by imperfect oxidation in the tissues, resulting in the production of lactic acid and perhaps of organic acids derived from imperfect protein metabolism.

We have no direct information concerning the part played by the kidney in phosphate retention, but renal insufficiency is suggested by the high blood ureas found in many of the cases in Table II. Further indirect evidence may be derived from the ammonia coefficient (and acid ratio). In certain cases of quite severe acidosis, the pH of the urine was not very low, while the ammonia

coefficient was only in the neighbourhood of 10 per cent. This implies that in spite of the presence of an excess of acid in the blood, acid substances were not being excreted adequately by the kidney. The relatively high pH does not suggest, however, that ammonia formation by the kidney was deficient.

Claussen (10) has found lactic acid increased in the blood in some cases of diarrhoea and vomiting—but by no means in all. He also mentions the presence in the urine of an organic acid which is insoluble in ether—possibly oxyproteic acid. Hartmann (11) also found lactic acid increased in the blood in some cases of diarrhoea and vomiting, but he showed that lactic acid, phosphoric acid, and acetone bodies, taken all together, would not account for the reduction of base bicarbonate. He suggests that either some unidentified acid must be present in the blood, or else that the acidosis must result partly from the excessive loss of base in the stools as compared with acid—a condition which is known to occur in some cases of diarrhoea. (Holt, Courtney and Fales (12).)

The treatment of this condition is based on the foregoing remarks. Marriott and Hartmann (13) hold that the restoration of the volume of the circulating blood is paramount ; the amelioration of the acidosis following as a consequence. They are of the opinion that the oral administration of salts and fluid is unsatisfactory on the grounds that mesenteric stasis interferes with absorption and renders treatment ineffectual. They recommend the administration of 5 per cent. glucose, with suitable amounts of sodium bicarbonate added, by the intraperitoneal or intravenous routes. It is clear, however, from the comparison of columns 7 and 18, that when alkali is given by mouth, an effective proportion is absorbed. Nevertheless, it must be admitted that large doses are required to produce an adequate response, and any part of the salt so given which is unabsorbed will remain in the bowel and tend to increase the diarrhoea. On the other hand, repeated intraperitoneal salines are not wholly desirable. Marriott and Hartmann deprecate the administration of large quantities of normal saline, because the concentration of chloride rises in the blood and tends to displace bicarbonate, with an increase in the existing acidosis. While this is true when saline is given alone, reference to Table II shows that when sodium bicarbonate is given simultaneously, the rise in plasma chloride is controlled.

There is, however, much to be said in favour of giving glucose solutions without sodium chloride for the relief of dehydration. For in the administration of glucose saline preparations, part of the water in the solution must be reserved for the osmotic requirements of the extra sodium chloride that has gained admission to the blood and tissues and will not be available for the relief of the existing dehydration. In the case of a pure glucose solution, on the other hand, at least part of the sugar will be oxidized in the ordinary processes of metabolism, and the water in which it was dissolved can be entirely diverted to make good the deficiency of fluid.

Claussen has drawn attention to the dangers of giving sodium bicarbonate in lactic acid acidosis, because in this condition excess of sodium lactate is produced in the blood. With the return of the circulation to normal, the lactic

acid is oxidized, giving rise to an excess of base which may cause a temporary but dangerous alkalaemia. (Cf. Table II, Cases 2 and 15.)

Superficially, the association of alkalaemia with the secretion of an acid urine appears paradoxical. We have observed its presence in congenital pyloric stenosis, and it has been found in a number of other conditions. In view of the interest attached to this association and the bearing it has on the pathology of diarrhoea and vomiting, its causation will be considered from a more general standpoint. The conditions in which the pH of the urine is low, in spite of a high bicarbonate reserve and pH of the blood, may be classified as follows:

A. Vomiting present; toxaemia absent.
   1. Congenital pyloric stenosis (14).

B. Vomiting present, toxaemia probably present.
   1. Acquired pyloric stenosis (15).
   2. Non-obstructive vomiting (14).
   3. Acute infantile diarrhoea and vomiting.
   4. High intestinal obstruction.
   5. Hydrazine sulphate poisoning. (Experimental (16).)

C. Vomiting absent; renal disease possibly present.
   1. Certain cases of nephritis and diabetes treated with alkali (17).

D. Vomiting, toxaemia and renal disease absent.
   1. After severe haemorrhage (18).
   2. Condition produced by the experimental injection of sodium phosphate (19).

It will be seen from the above classification that the association of alkalaemia with the excretion of an acid urine can occur in the absence of toxaemia and renal disease. Thus, in congenital pyloric stenosis, it depends entirely on the loss of chloride from the body. While, therefore, in some of the other conditions it is possible that kidney damage is a factor, it is probable that loss of chloride plays the more important part, even in those conditions where active base retention by the kidney might occur.

In congenital pyloric stenosis we have usually found an alkalaemia low blood chloride and an alkaline urine. Such findings are easily comprehensible. Loss of hydrochloric acid from the stomach leaves an excess of base in the blood, which combines with carbon dioxide to form bicarbonate. The excess of bicarbonate is then excreted in the urine, to an extent which is limited by the osmotic requirements of the blood. The secretion of an acid urine under these circumstances in some of these cases may be explained on the line of reasoning set out by Marriott and Hartmann (13) and by Hartmann (14). These writers, basing their conclusions partly on the work of Gamble on base retention in starvation and in experimental pyloric stenosis (20, 21), state: 'It has been shown, for instance, that the body tends very strongly to maintain its normal fixed base concentration and in certain conditions the fixed base of the blood is maintained irrespective of the hydrogen-ion concentration. . . . The preservation of a normal osmotic pressure within the cells appears to be of even greater import than the maintenance of a normal hydrogen-ion concentration.' They

point out that electrolytes contribute more than 90 per cent. of the osmotic pressure of the blood, but that when these electrolytes are reduced, the non-electrolytes, and notably urea, attain special importance. Again, discussing the alkalaemia produced by vomiting (14), Hartmann's conclusions are that chloride is lost by vomiting. That as chloride diminishes in the blood, bicarbonate is retained and compensates partly for the deficiency of osmotic pressure. That when the loss of sodium chloride in the blood is not fully replaced by sodium bicarbonate, the non-protein nitrogen is raised and may keep the osmotic pressure normal. That when the sodium bicarbonate content of the blood is high, there is a depression of respiration sufficient to lead to the accumulation of enough carbonic acid to maintain an approximately normal $\frac{H_2CO_3}{NaHCO_3}$ ratio, so that the reaction of the blood (pH) is usually nearly normal. Following increased pulmonary ventilation from any cause, however, the blood becomes abnormally alkaline, and manifestations of tetany may appear. That when the deficiency of sodium chloride in the blood disappears as a result of the administration of sodium chloride, the excess of non-protein nitrogen and sodium bicarbonate in the blood is rapidly excreted by way of the urine. That the excretion of sodium bicarbonate, sodium chloride, and non-protein nitrogen depends on the total concentration of crystalloid (electrolyte and non-electrolyte) in the blood. When this concentration is less than normal, sodium bicarbonate is retained in the blood, and the urine remains acid in reaction, despite the presence of a greatly increased plasma carbon dioxide content. That marked vomiting without actual organic pyloric or intestinal obstruction may lead to identical chemical changes. That loss of gastric or intestinal secretion by way of fistulae results in the same chemical changes as does vomiting.

The explanation of the persistence of the acidity of the urine in the presence of alkalaemia is found in the sixth of Hartmann's conclusions, and this explanation is applicable to any of the conditions in the classification where vomiting is present; pyloric stenosis, intestinal obstruction, and hydrazine poisoning. Its occurrence in conditions not associated with vomiting may be explained in a similar manner.

It has already been pointed out that base retention may occur in the absence of kidney disease, and further proof of this is furnished by the experiments of Hendrix and his co-worker on sodium phosphate injections in dogs, and by Evans on experimental anaemia. The reasons for both of these findings may be derived from Hartmann's conclusions. Thus the alkalinity of the blood after haemorrhage may be associated with the dilution effect which restores the blood volume to normal.

The principles enunciated by Hartmann will now be applied to the discussion of diarrhoea with vomiting, and alkalaemia.

The alkalaemia which occurs in diarrhoea is of an unusually high degree and differs from the preceding examples in the length of time it lasts without the administration of alkaline salt or other drug. In some of these cases

vomiting was not a prominent feature, indeed, in Cases 4 and 8 it was practically absent, so that loss of hydrochloric acid from the stomach was not important. The alkalosis, however, may be explained partly by the loss of acid from the bowel exceeding the loss of base. But leaving the latter possibility aside, it is probable that loss of sodium chloride through the bowel would lead to a low chloride level in the blood. In order to maintain the osmotic pressure of the plasma, therefore, the kidneys would retain the constituents of the plasma as far as possible. Chloride is retained, but it appears that phosphate cannot be retained by the normal kidney, except in very small amount. Both base chloride and phosphate are being lost in the faeces, but the increased salt loss mainly falls on the base chloride; the loss of base phosphate is much less. Hence the need for excretion of phosphate and sulphate by the kidney still exists; the sulphate must be excreted with its full quota of fixed base, but the base corresponding with the phosphate can be retained—provided that a urine of maximum acidity is excreted and in which the base is largely supplied by the kidneys in the form of ammonia. Reference to Table III shows that these conditions are in fact frequently fulfilled.

The possibility of base retention due to kidney disease cannot, of course, be excluded, but it is difficult to explain the persistence of alkalosis for weeks after alkali administration has ceased on the grounds of deficient renal excretion alone. Also, there was less evidence of renal disease in the alkalaemic than in the acidaemic cases. Moreover, even in those cases of kidney disease and diabetes where the secretion of an acid urine coincides with an increase in plasma bicarbonate, one need not ascribe the high alkali reserve to the inability of the kidney to excrete base. The chloride content of the blood is often low in these conditions, and the base retention may be secondary to chloride depletion. It thus seems possible that the appearance of acidaemia or alkalaemia in acute diarrhoea depends on the relative loss of water and salt: when the loss of water predominates, acidaemia and anhydraemia will be found; where the loss of salt in proportion to the loss of water is outstanding, alkalaemia with an acid urine will result, until such time as the osmotic pressure of the plasma is restored, when the urine will become alkaline. This generalization is supported by the observation that in acidaemic cases, after centrifugalizing, the volume of red cells relative to plasma was high, whereas in these alkalaemic cases the reverse was the case—even when the general aspect of the infant was one of slight dehydration, the relative volume of red cells was normal or less than normal. Most of the observations were roughly gauged by eye, but in Case 5, Table III, the most dehydrated of the alkalaemic infants, an accurate haematocrit determination showed that the red cells only occupied 22·5 per cent. of the blood-volume.

In neither acidaemic nor alkalaemic cases did the blood urea seem to play much part in adjusting the osmotic pressure: in acidosis with anhydraemia it was frequently very high, while even in alkalaemic cases, deficient in plasma chloride, it was sometimes low. It seemed likely that the chief factor in urea retention was renal incompetence.

From what has already been said, it follows that the association of a high plasma bicarbonate with a low plasma chloride may be interpreted in one of two ways:

1. Chloride has been lost by excretion through the bowel, and the base bicarbonate is raised to compensate for the fall in osmotic pressure. If the osmotic pressure has been very low, the retention of base may be so marked as to leave the urine acid. (Table III.) If the osmotic pressure, however, is raised to normal limits by the base bicarbonate, the necessity for further retention is at an end, and the excess of base appears in the urine. (Table IV, 5, 6, and 7.) Under the above circumstances, the chloride content of the urine is low. The condition of these patients is improved by the administration of sodium chloride.

2. Sodium bicarbonate has been given as a therapeutic measure—but to excess. Chloride is displaced into the urine, which accordingly contains it in relatively large quantities. (See Case 15, Table II, September 18, 26, and 27; Case 17, Table II, October 17 and 22; and Case 10, Table IV, October 2.) The indication is to cease giving alkali. In two cases of this type, administration of sodium bicarbonate was followed by the appearance of oedema. Cessation of alkali was followed by the copious excretion of a urine rich in chloride, but otherwise very dilute, together with the rapid disappearance of the oedema.

Haden and Orr (22) have suggested that the *low* plasma chloride in intestinal obstruction is due to migration of chloride to the tissues, as part of a protective mechanism. In diarrhoea with alkalaemia and low plasma chloride, there is no evidence in favour of the passage of chloride to the tissues. On the contrary, the ratio of red cell chloride to plasma chloride is less than normal, and the chloride content of the liver and kidneys *post mortem*, in two alkalaemic cases, was lower than that found in acidaemic cases. Further observations are required to make this point conclusive.

Just as excess of bicarbonate displaces chloride, so excess of chloride may displace bicarbonate from the blood; such an occurrence would account for the moderate acidity of urines in some cases of anhydraemia with acidosis, but it does not explain the frequent absence of chloride from the urines in these conditions.

It is important to notice that in acidosis both the plasma bicarbonate and chloride may be reduced; this does not mean that the osmotic pressure of the blood is necessarily lowered, for reduction of plasma bicarbonate does not always involve loss of plasma base. It is probable, under these circumstances, that the osmotic pressure of the blood is more than maintained by combination of the base with lactic and other acids, and by the concentration of such salts through the loss of fluid through the bowel.

Certain of the statements made in the preceding paragraphs dealing with alkalaemia with acid urine will now be illustrated by a fuller consideration of Case 8, Table III. This patient looked moderately ill on admission; the diarrhoea was not of extreme severity and vomiting was absent, but in view of the low plasma chloride, a bad prognosis was given. The routine administration of alkali caused an extraordinary rise in the plasma bicarbonate; presumably

there had been previously a grave deficiency in the osmotic pressure of the blood. Alkali was now stopped, and thereafter the plasma bicarbonate reserve fell and the chloride rose. In order to hasten this process, eight grains of ammonium chloride were given; the rise in plasma chloride and fall in the bicarbonate continued. By this time (October 10) the urine had become alkaline; presumably the restoration of the osmotic pressure of the blood allowed the excess of base to be excreted.

On November 5, halogen salts had also reappeared in the urine and the plasma bicarbonate had fallen to 0·0152 molar. The sequence of events makes it highly probable that these changes must be associated with the administration of eight grains of ammonium bromide on the 21st and a similar quantity on the 29th of October, and the effect of ammonium halide in cases of this type, in which no alkali is being given, would appear to be more marked than in cases of acidosis, treated with alkali at the same time as the ammonium salt therapy. Indeed the fall in alkali reserve after the administration of ammonium chloride is so great that it is difficult to believe that the diminution has been brought about by these means alone.

In view of the acidosis now present, alkali was again given in small quantities; within a few days the condition of alkalaemia and acid urine was restored. The patient gradually got weaker and died. No lactic acid was found in the urine of this patient; it was sought on November 12 and 13 only.

In view of the high urinary phosphate found on October 18, the inorganic phosphorus of the blood was estimated and found to be high; 10·2 mg. It was thought that this represented an attempt to maintain the osmotic pressure of the blood by raising the level of phosphate, but that the mechanism was doomed to failure because the excess of phosphate over normal led to the excretion of the extra phosphate in the urine. If such were the case, one might expect, in the long run, a depletion of body phosphate. By November 5 the blood phosphorus had fallen to 4·5 mg. and the urine phosphate to 0·53 per cent. On November 12 the blood phosphorus was only 2 mg. per cent. while the urine next day contained but 0·035 phosphate. The injection, subcutaneously of three ounces of isotonic phosphate solution at pH 7·2, temporarily increased the phosphate content of the urine, but two days later this had fallen again to a very low figure, and within a few days the patient died.

The findings in this case bear a striking resemblance to those obtained by Gamble (21) in experimental pyloric obstruction where there was a rise of plasma bicarbonate and a fall in plasma chloride. In some of his cases the inorganic phosphorus of the blood was also slightly increased, and he suggests that the object of this increase was to compensate for the lowered osmotic pressure of the blood; although, as he points out, the change effected thereby is very small.

Another interesting feature of Case 9, is the pH of the blood, which was never as high as would have been expected from the bicarbonate content. This, possibly, partly depends on an increase of base equivalence of the plasma protein at lower hydrogen-ion concentrations (Gamble), but chiefly to an increase of

carbon dioxide. The increase of carbon dioxide would also help to maintain the osmotic pressure of the blood, in addition to the increase due to the high base bicarbonate content.

Gamble also confirms the value of sodium chloride administration in pyloric stenosis and prefers it to ammonium chloride because, although both substances increase the blood chloride and lower the bicarbonate, part of the ammonium chloride is excreted as such by the kidneys; this causes diuresis, and is undesirable in animals which have already lost much fluid by vomiting. By analogy, ammonium salts should be avoided in diarrhoea and saline preferred.

The Chloride Content of the Cerebro-spinal Fluid.

The cerebro-spinal fluids were collected *post mortem* in a few cases of diarrhoea and vomiting and the chloride content estimated. The results are shown in Table V. The plasma chloride and bicarbonate figures given were the last obtained before death.

It will be seen that in Cases 1 and 6 the chloride in the plasma and cerebro-spinal fluid is very low—a finding which is supposed to be characteristic of meningitis; no meningitis was observed *post mortem* in either of these cases. On the other hand, the cerebro-spinal fluid of Nos. 4, 7, and 8 was normal, although the plasma chloride was reduced.

Conclusions.

1. In most cases of infantile diarrhoea and vomiting an acidaemia is present, but in some an alkalaemia may be found. In the latter the reduction in the osmotic pressure of the blood is often so great, that a retention of base occurs, leading to the excretion of an acid urine.

2. If the urine is neutral or alkaline, or the ammonia coefficient is below 8 per cent., or the ammonia combined acid is less than twice as great as the titratable acid, then acidosis is probably absent. In these circumstances, if chloride is persistently absent from urines of average concentration, it is probably advantageous to give extra sodium chloride by mouth or by some other route, and it is probably unsafe to administer alkali.

3. If the urine is acid and the ammonia coefficient is above 8 per cent. and the ratio of ammonia combined acid to titratable acid is greater than 2·5, acidosis is not necessarily present, and the bicarbonate reserve of the blood may even be increased.

4. The prognosis of a case cannot be gauged from the level of the plasma bicarbonate. Certain cases with great depletion of the alkali reserve of the blood rapidly improved, while, on the other hand, the plasma bicarbonate was only moderately lowered in some cases of the utmost severity.

We are indebted to Dr. Eric Pritchard, the Medical Director, and to the Medical Staff of the Infants' Hospital, who have kindly allowed us to investigate the cases under their care, for much helpful criticism.

TABLE II.

Case No.	Date.	Remarks.	Motions.	Vomits.	Blood.				Urine.								Therapy.		
					pH.	Plasma bicarb. (molar).	Plasma Cl (as NaCl).	Urea.	pH.	Titratable acid.	NH_3-combined acid.	Ratio.	Urea.	NH_3 coefficient.	Chlorides.	Phosphates.	$NaHCO_3$ or NH_4Br or $[NH_4Cl]$ (in grains) Oral.	Rectal.	Subcut.
1	27.3	F. H. 9 lb. Marasmic; pale; dehydrated; respirations rapid	4	4	7·205	0·0073	—	—	—	—	—	—	—	—	—	—	—	—	—
	28.3	Respirations slower	6	1	7·315	0·022	—	—	—	—	—	—	—	—	—	—	27	77	7
	29.3	Colour grey. Died	5	0	7·305	0·016	—	—	—	—	—	—	—	—	—	—	67	5	—
2	6.5	L. L. 8 lb.; 4½ months; pale; drowsy	7	3	—	0·0059	—	—	—	—	—	—	—	—	—	—	0	—	—
	7.5	Trace of acetone in urine. Blood phosphate 3·2 mg. per 100 c.c.	7	0	7·31	0·0213	—	—	5·2	70	126	1·8	1·6	22·0	—	—	63/1	22/1	—
	9.5	Trace of acetone in urine. Blood phosphate 3·5 mg. per 100 c.c. Improved	5	0	7·445	0·0320	—	—	5·8	44	89	2·2	2·3	10·8	—	—	0	—	—
	14.5	—	6	0	—	0·022	—	—	6·3	5	22	4·4	0·9	6·6	—	—	0	—	—
3	10.5	H. B. 7 lb.; 3½ months; pale; dehydrated. No ketonuria	8	0	7·205	0·0138	—	—	6·2	24	82	3·4	1·9	12	—	—	50/3	—	—
	14.5	—	5	0	—	0·0060	—	—	—	—	—	—	—	—	—	—	34/3	—	—
	15.5	Slight general rigidity. No acetonuria	10	0	—	0·029	—	—	5·6	20	146	7·3	1·1	37	—	—	150/2	—	6/1
	17.5	Rigidity less. Blood phosphate 7·2 mg. Died	8	0	—	0·016	—	0·066	5·4	44	114	2·6	2·3	14	—	—	140/2	—	4/1

4	1.6	F. M. 10 lb.; 5½ months; Moderate marasmus. No ketonuria; blood phosphate 4·72	—	—	—	0·025	—	—	—	2	8	4·0	1·2	1·9	—	—	120/4	—	—
	7.6	Diarrhoea contracted on 3.6	3	2	—	0·011	—	—	—	—	—	—	—	—	—	—	120/5	—	—
	9.6	Restless	5	2	—	0·022	—	—	—	—	—	—	—	—	—	—	150/3	—	—
	11.6	Pale, sunken and collapsed	5	2	—	0·0146	—	—	—	—	—	—	—	—	—	—	133/3	—	—
	21.6	Died	7	0	—	0·0167	—	0·325	6·4	6·5	82	11·2	0·9	25	—	—	340/11	—	—
5	24.5	N. S. 7½ lb.; 3 months. 3 days' history; marasmic	—	—	—	0·0205	—	—	—	—	—	—	—	—	—	—	120/10	—	—
	3.6	—	6	0	—	0·0136	—	—	—	—	—	—	—	—	—	—	—	—	—
	5.6	Sudden gain of ½ lb. in wt. Died suddenly 2 days later	—	—	—	0·030	—	—	—	—	—	—	—	—	—	—	162/2	20/2	8
6	8.6	J. B. 7 lb.; 6 weeks; marasmic	4	1	—	0·0130	—	—	—	—	—	—	—	—	—	—	48/7	—	—
	11.6	Diarrhoea and vomiting have been much worse	7	4	—	0·0100	—	0·38	—	—	—	—	—	—	—	—	134/3	—	—
	136	Slightly improved; urine contains trace of albumin and sugar, no acetone	3	3	—	0·022	—	—	5·8	30·	49	1·63	1·35	10·5	—	—	96/2	3/1	—
	15.6	Some head-retraction; dehydrated. Died	4	6	—	0·0119	—	—	—	—	—	—	—	—	—	—	43/2	—	—
7	4.6	J. S. 7 lb.; 4 months; 5 days' history.	4	1	—	0·012	—	—	—	—	—	—	—	—	—	—	62/3	—	8/2
	5.6	No ketonuria	8	0	—	0·014	—	0·035	6·0	35	125	3·6	2·4	14·6	—	—	39	—	—
	7.6	From 5th–6th gained ½ lb. Slight oedema. Pus and casts in urine. Died.	5	0	—	0·0195	—	—	—	—	—	—	—	—	—	—	98/2	—	4
8	29.6	C. P. 5 months; 3 days' history. Trace of acetone in urine.	7	0	—	0·0132	—	0·045	6·0	37	80	2·17	1·95	11·5	—	—	—	—	—
	1.7	Worse. Died	8	0	—	0·0315	—	—	—	—	—	—	—	—	—	—	128/2	—	5/2

TABLE II (*continued*).

Case No.	Date.	Remarks.	Motions.	Vomits.	Blood. pH.	Blood. Plasma bicarb. (molar).	Blood. Plasma Cl (as NaCl)	Blood. Urea.	Urine. pH.	Urine. Titratable acid.	Urine. NH_3-combined acid.	Urine. Ratio.	Urine. Urea.	Urine. NH_3 coefficient.	Urine. Chlorides	Urine. Phosphates.	Therapy. $NaHCO_3$ or NH_4Br or $[NH_4Cl]$ (in grains). Oral.	Therapy. Rectal.	Therapy. Subcut.
9	30.6	B. M. 6 lb.; 2 weeks; 10 days' history. Dehydrated	10	4	—	0·0080	—	—	—	27	75	2·77	1·38	15·1	—	—	53/2	7/1	4/1
	3.7	—	4	0	—	0·0292	—	0·028	—	—	—	—	—	—	—	—	207/3	—	29/2
	5.7	Oedema of hands, feet, and vulva; mucosae dry. Died	8	0	—	0·017	—	0·033	6·0	8	21	2·6	0·64	9·3	—	—	40/1	—	—
10	10.7	A. H. 4½ months; vomiting 14 days; diarrhoea 2 days. Very dehydrated; pale	5	2	—	0·010	—	0·13	—	—	—	—	—	—	—	—	180 IX	—	9
11	14·8	A. A. 8 lb.; 2 months. Acetone ±	2	0	—	0·0167	—	0·016	—	29	125	4·3	1·2	28	—	—	—	—	—
12	22.8	W. 10 lb.; 3 months; 4 days D. and V. Very ill. Cyanosed; Resps. 60. Pulse feeble. Died	—	—	—	0·0052	—	0·48	—	—	—	—	—	—	—	—	—	—	—
13	17.8	J. B. 17 lb.; 10 months; 7 days' history; dehydrated; colour dusky	4	0	—	0·0163	—	—	—	—	—	—	—	—	—	—	—	—	—
14	1.9	L. B. 8¼ lb.; 2⅔ months. Pale and dehydrated	5	2	—	0·0110	—	—	6·2	45	129	2·9	2·7	13·4	—	—	—	—	—
	4.9	Worse after temporary improvement. Acetonuria. Died	10	1	—	0·0197	—	—	6·0	13	86	6·5	0·5	48	—	—	122/3 VIII	—	22/2

15	17.9	P. B. 11 lb.; 6 months; 2 days' history; dehydrated; ashy grey; extremities cold; toxic; drowsy	2	1	—	0·0063	0·58	0·12	—	—	—	—	—	—	—	—	—	—	—
	18.9	Colour improved; restless	6	5	—	0·0240	0·55	—	—	—	—	—	—	—	—	—	60	—	—
	24·9	—	6	0	—	0·0252	0·52	—	7·0	6	90	15	2·3	11	0·042	—	100/6	—	20/6
	26.9	Oedema of hands, feet, and face; resps. rapid; face flushed	4	0	—	0·0325	0·53	—	7·0	0	33	—	0·93	10	0·23	—	40/2	—	37/2
	27.9	Oedema increased	7	0	—	0·0360	0·48	—	—	—	—	—	—	—	—	—	0	—	—
	28.9	Oedema less	5	0	—	—	—	—	8·1	0	17	—	0·27	—	0·302	0·045	—	—	—
	29.9	Oedema disappearing; condition improved	5	0	—	0·022	0·58	—	—	—	—	—	—	—	—	—	—	—	—
16	26.9	A. B. 10 lb.; 4 months; 3 days' history; dehydrated	9	4	7·28	0·0092	0·64	—	6·2	32	186	5·8	3·9	12·6	0	—	48/2	—	12/2
	27.9	Slight cyanosis. Died	—	—	—	0·0167	0·63	—	—	—	—	—	—	—	—	—	105	—	12
17	4.10	M. D. 9½ lb.; 4 months; 4 days' history; cyanosed; extremities cold; apparently moribund	2	1	7·14	0·0035	0·41	—	—	—	—	—	—	—	—	—	—	—	—
	5.10	Much improved	6	0	7·39	0·0240	0·54	—	4·8	12	35	2·9	1·35	7·2	0	0·152	72	5	5
	8.10	—	6	1	7·33	0·0151	0·57	—	6·1	5	38	7·6	0·4	26·5	0·061	—	—	—	—
	10.10	Trace of acetone in urine	6	3	7·24	0·0143	0·59	—	5·8	11	142	13·0	1·17	33·7	0·192	0·087	50	—	—
	12.10	—	9	0	—	0·0263	0·61	—	—	—	—	—	—	—	—	—	135/2 VIII	—	—
	15.10	Drowsy and dehydrated	6	0	7·17	0·0056	0·66	—	—	—	—	—	—	—	—	—	90/3	—	—
	17.10	Slow improvement began and continued	9	0	7·23	0·0138	0·66	—	6·0	15	139	9·2	1·75	22·2	0·231	—	60/2	—	—
	22.10	—	7	0	7·45	0·0291	0·49	—	—	—	—	—	—	—	—	—	150/5 VIII	—	—
	24.10	—	6	0	7·41	0·0297	0·58	—	7·0	0	10	—	0·4	7·0	0·037	0·074	60/2 VIII	—	—
	30.10	—	7	0	—	—	—	—	7·5	0	54	—	0·7	21·5	—	0·108	—	—	—

TABLE II (*continued*).

Case No.	Date.	Remarks.	Motions.	Vomits.	Blood. pH.	Blood. Plasma bicarb. (molar).	Blood. Plasma Cl (as NaCl).	Blood. Urea.	Urine. pH.	Urine. Titratable acid.	Urine. NH_3-combined acid.	Urine. Ratio.	Urine. Urea.	Urine. NH_3 coefficient.	Urine. Chlorides.	Urine. Phosphates.	Therapy. $NaHCO_3$ or NH_4Br or $[NH_4Cl]$ (in grains). Oral.	Therapy. Rectal.	Therapy. Subcut.
18	8.10	A. H. 14½ lb.; 5 months; 24 hours' history. Moderate dehydration; trace acetone in urine	3	0	7·38	0·0195	0·63	—	6·3	21	95	4·5	1·5	17·7	0·057	—	—	—	—
19	8.10	M. O. 7 lb.; 4 months; 2 weeks' history of vomiting	7	2	7·23	0·0133	0·66	—	—	—	—	—	—	—	—	—	80/3 XVI	18/1	—
	11.10	—	8	3	7·30	0·0139	0·56	—	5·4	20	57	2·85	1·8	8·9	0·035	0·104	16/3	—	—
	13.10	Condition fairly good. Collapsed and died with convulsions on 14.10.28	4	0	—	0·0296	0·52	—	—	—	—	—	—	—	—	—	90/2 XVI/2	29/2	—
20	9.10	A. G. 5 months; 3 weeks' history D. and V. Very dehydrated. C. S. F. at P.M. = 0·475 NaCl. Died	—	—	—	0·0056	0·40	—	—	—	—	—	—	—	—	—	—	—	—
21	25.10	A. F. 22 lb.; 15 months; collapsed and dehydrated. Skin cold and clammy	4	3	7·31	0·0113	0·63	—	5·8	82	220	2·68	2·6	23·6	0·025	1·0	—	—	—
	27.10	Still collapsed and dehydrated. Acetone in urine.	2	4	7·42	0·0250	0·55	—	6·0	48	182	3·8	4·2	12·1	0·06	0·46	45	—	10
22	5.11	R. H. 8 lb.; 5½ months; 5 days' history of diarrhoea; very dehydrated	8	2	7·25	0·014	0·47	—	—	—	—	—	—	—	—	—	48/5	—	22/1
	6.11	No acetone in urine	8	1	—	—	—	—	5·2	40	150	3·76	2·4	17·4	0·308	0·346	—	—	—
	7.11	Died	—	—	7·23	0·0079	—	—	—	—	—	—	—	—	—	—	62/2	8	20/1

23	7.8	J. L. 12 lb.; 5 months. 4 days' history of D. and V.; pallor; moderate dehydration	—	—	—	0·0120	—	—	—	—	—	—	—	—	—	—	—	—	—
	8.8	—	10	0	—	0·0316	—	—	8·0	0	20	—	1·6	3·5	—	—	90/2	—	—
	10.8	Improved, but diarrhoea recommenced 9 days later	8	0	—	0·0240	—	—	—	—	—	—	—	—	—	—	35/2	—	—
	29.8	Pale and dehydrated	8	1	—	0·0406	—	—	7·6	—	—	—	—	—	—	—	73/1	—	—
	1.9	More dehydrated. Died	12	4	—	0·0290	—	—	6·5	5	14	2·8	0·57	6·8	—	—	72/2	—	—
24	15.8	J. H. 8¾ lb.; 3 months. 1 weeks' history of D. and V. Collapsed; cold, pale and dehydrated	3	1	—	0·0140	—	—	6·0	16	127	7·9	1·8	19·0	—	—	—	—	—
	17.8	Collapsed; pale. Died	7	1	—	0·0131	—	0·18	—	—	—	—	—	—	—	—	124/2	7/1	—
25	24.8	H. M. 4¾ lb.; 3 weeks. 3 days' history of D. and V. Collapsed, wasted, dehydrated; face grey; panting; fits before admission. No acetonuria	7	5	—	0·0094	—	0·167	4·8	56	116	2·1	0·97	33·5	—	—	—	—	—
	27.8	Collapsed; grey; dehydrated; abdomen distended. Died	7	11	—	0·0327	—	0·220	—	—	—	—	—	—	—	—	158/3	12/2	11/2
26	19.10	A. B. 17½ lb.; 1 year. Rather dehydrated	4	2	7·27	0·012	0·56	—	—	—	—	—	—	—	—	—	37	—	—
	2.11	—	—	—	7·4	0·025	—	—	6·4	12	59	4·9	0·73	22·7	0·028	0·84	37	—	—
27	2.10	F. B. 7 lb.; 11 weeks. 1 week's history. Very dehydrated	9	1	7·33	0·018	0·58	0·32	5·4	37	130	3·5	2·7	13·5	0·56	—	50	—	6
28	17.9	P. P. 5¾ lb.; 1 month. D. and V. 9 days. No acetonuria. Died	—	—	—	0·011	—	—	6·0	65	140	2·15	1·9	20·6	—	—	—	0	—

TABLE III.

Case No.	Date.	Remarks.	Motions.	Vomits.	Blood. pH.	Blood. Plasma bicarb. (molar).	Blood. Plasma Cl (as NaCl)	Blood. Urea.	Urine. pH.	Urine. Titratable acid.	Urine. NH_3-combined acid.	Urine. Ratio.	Urine. Urea.	Urine. NH_3 coefficient.	Urine. Chlorides.	Urine. Phosphates.	Therapy. $NaHCO_3$ or NH_4Br or $[NH_4Cl]$ (in grains). Oral.	Therapy. Rectal.	Therapy. Subcut.
1	12.3	R. F. Marasmus; D. and V.—14 days. Very toxic	4	4	7·4	0·030	—	—	—	—	—	—	—	—	—	—	68/2	—	—
	15.3	Respirations moderate; acetone and diacetic acid in urine. Died	6	7	7·34	0·033	—	—	5·2	—	—	—	—	20	—	—	240/3	—	—
2	30.5	McC. 7 lb.; 10 weeks. 6 days D. and V. Pale and dehydrated; urates + + No acetone in urine. Died	11	7	—	0·042	—	—	6·0	—	—	—	—	—	—	—	540/7	27/7	30/7
3	21.8	F. C. 11½ lb.; 6⅔ months. Pale and sunken eyed	6	6	—	0·0275	—	—	5·6	81	138	1·7	3·0	13·0	—	—	0	—	—
	22.8	Urates in urine; no acetone. Some bronchitis	8	2	—	0·0370	—	0·016	5·2	110	105	0·95	3·65	7·9	—	—	73/1	—	—
	24.8	—	7	0	—	0·0380	—	—	—	0	6	—	0·8	2·1	—	—	70/2	—	—
	3.9	—	5	0	—	0·0237	—	—	7·6	0	12	—	0·94	3·5	—	—	36/11	—	—
4	5.9	R. G. 13 lb.; 7 months; 1 week's history. Fontanelle collapsed; no acetonuria	6	0	—	0·0330	—	0·025	5·4	94	52	0·55	1·7	8·6	—	—	0	—	—
	7.9	Much improved	10	0	—	0·0402	—	—	8·0	—	—	—	—	—	—	—	158/2	—	—

5	15.9	R. B. 11½ lb.; 3 months. Vomiting 11 days; diarrhoea 8 days. Collapsed and dehydrated; complexion dusky	4	0	—	0·0410	—	0·075	5·0	28	90	3·2	1·3	19·4	—	—	8	8	9
	16.9	Drowsy; twitching, flushed; extremities warm; plasma calcium 8 mg. %	4	7	—	0·0356	—	0·122	4·8	80	94	1·3	1·37	19·2	—	—	51	—	18
	18.9	No cyanosis or peripheral stasis. Resps. somewhat rapid; oliguria. Died	3	7	—	0·0400	—	0·210	5·0	60	88	1·5	1·27	20·0	0	—	56	—	25
6	21.9	E. S. 13 weeks. Moderate dehydration; pallor; meningismus; athetosis; restless; (morning urine)	8	0	—	—	—	—	6·0	57	80	1·4	1·12	20·0	0·069	—	—	—	—
	21.9	Later	—	—	—	0·0416	—	—	4·8	48	50	1·02	0·9	15·6	0·057	—	32	—	26
	21.9	6 p.m. less dehydration	—	—	—	—	—	—	5·0	43	30	0·7	1·05	8·0	0·042	—	—	—	26
	24.9	Eyes sunken; pallor	7	1	—	0·053	—	—	5·3	26	42	1·6	1·7	7·0	0·024	0·10	—	108/3	—
	26.9	Very restless; pallor	7	4	7·56	0·058	—	—	6·0	12	25	2·1	0·8	8·7	0	—	—	8/2	8
	28.9	Trace of albumin in urine; no acetone. Died	8	2	—	0·046	—	—	5·2	26	60	2·3	2·1	8·0	0	0·2	—	—	—
7	21.9	A. W. 18 lb.; 7⅓ months; 3 weeks' history. Looks flushed; meningismus and athetosis. Rigid	6	0	—	—	—	—	6·6	20	10	0·5	0·38	7·4	0·021	—	38/6 VIII/2	—	—
	25.9	Improved till 27th	5	1	7·47	0·033	0·57	—	5·5	49	28	0·57	2·2	3·5	0·017	Trace	45	—	—
	27.9	Head retraction; restlessness; urates in urine. No acetone (24 hours specimen)	5	2	—	—	—	—	5·0	74	168	2·6	2·2	21·5	0	0·40	?	—	—
	28.9	Head retraction; restlessness.	7	5	—	0·026	0·4	—	—	—	—	—	—	—	—	—	—	—	—

TABLE III (*continued*).

Case No.	Date.	Remarks.	Motions.	Vomits.	Blood. pH.	Blood. Plasma bicarb. (molar).	Blood. Plasma Cl (as NaCl)	Blood. Urea.	Urine. pH.	Urine. Titratable acid.	Urine. NH_3-combined acid.	Urine. Ratio.	Urine. Urea.	Urine. NH_3 coefficient.	Urine. Chlorides.	Urine. Phosphates.	Therapy. $NaHCO_3$ or NH_4Br or $[NH_4Cl]$ (in grains). Oral.	Therapy. Rectal.	Therapy. Subcut.
8	27.9	L. A. 15 lb.; 5 months; 10 days' history. Pale; listless; moderately ill; slight dehydration	5	1	7·43	0·0240	0·42	—	—	110	84	0·76	1·62	14·5	0	1·46	0	0	0
	1.10	Slightly improved; urine: trace of acetone; urates + +	10	1	7·57	0·0520	0·40	—	5·8	36	11	0·45	1·28	3·5	0	0·27	210/3	—	—
	3.10	On 6.10 got worse; slight twitching of face and arms. Given chloral grs. iii on 6th and 7th	6	0	—	0·0460	0·45	—	6·0	21	30	1·43	1·8	4·6	0·082	0·146	70/2	—	—
	10.10	Urates + +	6	0	7·52	0·0362	0·46	—	7·5	0	24	—	—	—	0	—	[V/2]	—	—
	12.10	Urates + +	6	0	7·50	0·0310	0·49	—	5·6	102	108	1·06	1·65	21·5	0·02	0·81	[III/2]	—	—
	15.10	—	6	0	7·50	0·0335	0·53	—	5·8	163	149	0·91	3·05	13·8	0	1·15	—	—	—
	18.10	Blood phosphate 10·2 mg. %. No acetone in urine	7	1	—	0·0308	0·52	0·025	5·7	115	82	0·71	2·4	9·6	0	0·8	—	—	—
	22.10	Blood phosphate 5·5 mg. %. Sleepless and fretful	6	0	—	0·0278	0·53	—	6·3	4	7	1·7	0·47	4·0	—	—	VIII/1	—	—
	25.10	—	7	1	7·31	0·0200	0·61	—	5·6	57	80	1·4	0·86	26·0	0·263	0·51	—	—	—
	29.10	Blood phosphate 3·6 mg. %	6	2	—	0·0200	0·62	—	5·2	36	188	5·2	4·0	13·2	0·345	0·274	VIII/1	—	—
	1.11	—	6	1	—	0·0266	0·58	—	—	—	—	—	—	—	—	—	—	—	—
	2.11	Sugar 0·6 % in urine	6	0	—	—	—	—	5·6	48	221	4·6	3·1	20·0	0·450	0·325	—	—	—

	5.11	Blood phosphate 4·3 mg. %. Traces of sugar and albumin in urine. Dehydrated. Has had chloral grs. iii	8	0	—	0·0152	0·63	—	5·3	62	206	3·3	4·04	14·3	0·205	0·53	—	—	—
	7.11	Slightly improved	9	0	7·44	0·0302	0·55	—	5·6	32	112	3·5	3·8	8·3	—	—	—	—	—
	10.11	Urine contains sugar	9	1	7·49	0·0407	0·49	—	—	29	61	2·1	3·7	4·6	0	0·48	30/2	—	—
	12.11	Venous blood: P. 2 mg. %. Blood-sugar 0·120 (3 hours after feed)	9	1	7·45	0·0443	0·52	0·024	6·6	28	39	3·9	2·4	4·5	0	0·125	70/3	—	—
	13.11	Urine contains trace of sugar	12	0	—	—	—	—	6·7	8	38	4·7	1·7	6·2	0	0·035	—	—	—
	14.11	Became worse. Glycosuria 2 %. Blood-sugar 0·117 % ($2\frac{1}{2}$ hours after feed)	11	1	—	0·0388	—	—	—	62	60	0·97	2·0	8·4	0	0·52	—	—	—
	16.11	Died	—	—	—	—	—	—	5·2	10	49	4·9	1·62	8·5	0	0·082	—	—	—
9	16.10	G. E. $15\frac{1}{2}$ lb.; 11 months; 5 weeks' history. Listless and pale	4	0	—	0·0326	0·54	—	—	—	—	—	—	—	—	—	0	—	—
	17.10	—	3	1	—	—	—	—	6·0	42	224	5·3	3·2	19·6	0	—	—	—	—
	18.10	Cough	7	2	—	0·019	0·58	—	6·3	28	186	6·3	4·0	13·0	0	0·42	—	—	—
	29.10	Slow depreciation	9	2	—	0·021	0·51	—	5·4	46	134	3·4	3·9	9·6	0	0·42	—	—	—
	5.11	Much worse; dehydrated; very pale. To have extra NaCl (oral, rectal, and subcutaneous)	6	3	7·45	0·0364	0·35	—	6·3	28	62	2·2	2·73	6·35	0	0·42	25/3	—	—
	7.11	Slightly improved	7	0	7·47	0·0392	0·42	—	7·3	6	70	11·7	2·16	9·1	0·037	0·455	—	—	—
	12.11	Rectal and subcutaneous saline stopped on 9th	5	1	—	—	—	—	7·8	0	109	—	2·6	11·6	0	0·193	—	—	—
	13.11	Became worse	6	2	7·49	0·028	0·49	—	5·4	36	93	2·6	2·85	9·2	0	0·125	—	—	—
	11	Died	5	1	—	—	—	—	8·2	—	—	—	0·46	—	0	—	—	—	—
10	27.8	H. M. $4\frac{1}{2}$ lb.; 3 weeks; 6 days' D. and V. Slight dehydration. Died	6	2	—	0·0327	—	0·22	5·8	70	76	1·08	1·1	18	—	—	150/3	36/3	20/3

TABLE IV

Case No.	Date.	Remarks.	Motions.	Vomits.	Blood. pH.	Blood. Plasma bicarb. (molar).	Blood. Plasma Cl (as NaCl)	Blood. Urea.	Urine. pH.	Urine. Titratable acid.	Urine. NH_3-combined acid.	Urine. Ratio.	Urine. Urea.	Urine. NH_3 coefficient.	Urine. Chlorides.	Urine. Phosphates.	Therapy. ($NaHCO_3$ or NH_4Br or $[NH_4Cl]$ (in grains)) Oral.	Therapy. Rectal.	Therapy. Subcut.
1	19.12	G. P. 5½ lb.; 3 months; 3 weeks' history D. Much subcutaneous saline. Died	9	5	7·21	0·0125	0·76	—	—	—	—	—	—	—	—	—	0	17/3	59/3
2	10.10	J. H. 11 lb.; 9 months; 14 days' diarrhoea (average 6 daily)	4	0	7·33	0·0215	0·52	—	—	—	—	—	—	—	—	—	+ + +	—	—
3	3.10	R. H. 4 days	6	0	—	0·0252	0·44	—	—	—	—	—	—	—	—	—	0	—	—
4	28.9	W. O. 11½ lb.; 4½ months	9	0	—	0·0295	0·43	—	—	—	—	—	—	—	—	—	0	—	—
5	1.6	F. 11 weeks. Wasted; very pale and dehydrated. Hb=82% Red cells 6,400,000	2	0	—	0·046	—	Raised	7·2	0	30	—	0·8	4·6	0·006	0·200	0	—	—
6	21.9	H. H. 16½ lb.; 8 months; 2 weeks' history. Not dehydrated	5	0	—	0·0477	0·55	—	7·5	—	—	—	0·55	—	0·305	—	170/3	—	—
7	4.9	W. G. 8 lb.; 4½ months; 5 days' history of D. and V.	6	0	—	0·042	0·45	—	8·2	0	15	—	0 3	3·2	0·177	0·360	+ +	—	—
8	24.9	K. P. 10 lb.; 6 weeks; 1 week's D. and V. Very dehydrated. Died	6	2	—	0·032	0·64	—	—	—	—	—	—	—	—	—	54/1	3½/1	9/1

9	15.6	J. C. 7 lb.; 8 weeks; D. and V. 2 weeks. Pale, dehydrated, rigid, head retraction; slight convulsion on previous day	6	0	—	0·037	—	—	—	—	—	—	—	—	—	—	106/3	—	—
	19.6	Opisthotonos, rigid and drowsy	8	0	—	0·033	—	24	—	—	—	—	—	—	—	—	[III]	—	—
	20.6	Noon, after three divided doses of NH_4Cl grs. iii, still spastic. Died	6	5	—	0·0135	—	—	—	—	—	—	—	—	—	—	—	—	—
10	2.10	P. R. 9¾ lb.; 3 months; diarrhoea 1 week. Colour poor, some dehydration	6	0	7·48	0·032	0·52	—	7·6	0	91	—	0·37	6·9	0·153	0·07	56/1	—	—
	3.10	Fretful	7	2	—	0·028	0·63	—	7·4	0	10	—	0·19	14·7	0·153	0·051	7½/1 IV	—	—
	16.10	Colour grey, very dehydrated. Died	3	0	7·06	0·0081	0·60	—	—	—	—	—	—	—	—	—	223/13 XX	4½/1	19/3

TABLE V.

No.	Plasma Bicarb. Molar.	Plasma Chloride. %	C.S.F. Chloride. %
1	0·0056	0·40	0·47
2	0·0081	0·60	0·72
3	0·0167	0·62	0·77
4	0·0250	0·44	0·71
5	0·0330	0·64	0·70
6	0·0390	very low	0·54
7	0·0400	0·50	0·77
8	0·0466	0·42	0·71
9	0·023	0·83	1·04

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A REVIEW OF VISCEROPTOSIS AND ALLIED ABDOMINAL CONDITIONS ASSOCIATED WITH CHRONIC INVALIDISM[1]

PART I

By H. BEDINGFIELD

Introduction.

The condition in which an absence of well-being and a lack of energy accompanies persistent abdominal symptoms of no known pathology is one worthy of investigation. Though it never leads to a fatal termination, it nevertheless assumes considerable importance from the mass of suffering and the loss of economic efficiency it produces. Not that it has failed to receive consideration in the past; on the contrary, a vast literature has accumulated around this one condition. The magnitude of this literature is not obvious at first sight, and only becomes so when it is realized that conditions as diverse as nervous dyspepsia, nephroptosis, gastroptosis, visceroptosis, auto-intoxication, intestinal stasis, chronic appendicitis, caecum mobile, and others too numerous to mention merely represent different interpretations of a single-symptom complex. This view becomes evident by an unprejudiced study of the clinical material as it presents itself in general practice; and the conclusion seems inevitable that some common whole must underlie these diverse manifestations.

In the past many investigators have come to the same conclusion. This they reached by an intensive and specialized study of one side of the problem, and for that reason, presumably, failed to obtain the general assent the facts deserved. It has therefore seemed to me worth while to approach the problem from the wide angle of general practice. The latter offers a very special facility for the study of the condition, in that the genesis, progress, and termination can be followed by one observer in a way not possible in any other branch of medicine.

The Clinical Picture.

To portray the clinical condition in all its varied manifestations is no easy task, and I doubt if the words of Burton (92) in the *Anatomy of Melancholy* can be improved upon. He says: 'In this hypochondriacal or flatuous melancholy the symptoms are so ambiguous that the most exquisite physician cannot determine of the part affected; sharp belching, fulsome heat in the bowels, wind

[1] Accepted for the degree of M.D. in the University of Edinburgh.

and rumblings in the guts, vehement gripings, pain in the belly and stomach sometimes, after meat that is hard of concoction.' Cullen (153), writing of dyspepsia, merely puts the same idea into the formal language of science when he describes it as: anorexia, nausea, vomitus, inflatio, ructus, ruminatio, cardialgia, gastrodynia; pauciora saltem vel plura horum simul concurrentia plerumque cum alvo adstricta et sine alvi vel ventriculi ipsius vel aliarum partium morbo. We do not find, however, a clear description of an individual case representative of the condition as we know it to-day until that reported by Abercrombie (2) in 1830. He describes a woman 18 years of age suffering for a year or more from a disordered state of the bowels accompanied by remarkable tympanitic distension. She was also affected with a variety of hysterical symptoms, general weakness, and impaired appetite. These symptoms continued, improving at one time, getting worse at another, until finally a second stage of the illness was reached. She then developed aphthae in the mouth, and vomited from time to time thick white matter. The bowels became most obstinately constipated. This condition was accompanied by a sense of burning along the intestinal canal and a sensation of sinking in the stomach. Thirst and headache were prominent. There was also pain in the right side of the abdomen and along the ascending colon. Much viscid mucus and a white substance would then be passed by the bowel. She would have for a few days almost normal movements, whereupon the condition would recur. During these attacks the pulse never rose above 74–80. The bowel discharge varied from immense quantities of pure transparent jelly to long fibrous stringy matter and frequently large pieces of firm uniform tenacious membrane, often several inches long, in the form of a tube or enclosing small hard lumps of faeces. During the whole of this time the appetite was variable and the digestion bad. She would spend six or seven months in bed, and then on removal to the country recover considerably. On her return to town she would relapse. Finally she died of acute pulmonary tuberculosis. Abercrombie was able to examine her abdomen, in which he found the organs absolutely normal excepting the colon, which was studded with numerous small white vesicles, the size of a pin's head, from which, when punctured, exuded a small quantity of clear fluid.

Clifford Allbutt (9), in his lectures on the 'Visceral Neuroses', describing cases of gastralgia, enteralgia, &c., observed that these symptoms occurred in individuals of a temperament somewhat different from the ordinary. They were either hysterical, selfish, and introspective, or else over-conscientious, self-forgetful, and wearing themselves out for others. He regarded these different abdominal symptoms as manifestations of an abnormal central nervous system.

Glénard (233), impressed by the physical findings as well as the mental peculiarities which identified these cases, described a typical one as presenting: (1) asthenia and general depression; (2) a dragging feeling, a sense of weight or a sense of emptiness in the epigastrium; (3) a sense of burning in the stomach, sometimes accompanied by vomiting; (4) neurasthenic symptoms. Associated with them were the following physical signs: (1) deformity of the abdomen,

flabbiness of its walls, and a lack of resistance in the epigastrium; (2) splashing sounds in the stomach, epigastric pulsation, palpable kidney, caecum, transverse colon and sigmoid.

Treves (593) in England recognized a similar type. The patient, he writes, usually a woman, complains of certain asthenic symptoms, accompanied by general depression and a state of general ill-health. A condition of invalidism supervenes, rendering her unfit for any exertion until she becomes only comfortable when recumbent. She complains of a sense of weight and a dragging in the abdomen. There is pain in the back and continued weariness with a burning feeling in the epigastrium, vomiting, loss of appetite, and distress after food. The bowels are irregular, and constipation tends to be the rule. Pain is complained of when they act and aperients cause distress.

On the other hand, surgeons like Lane (374) were impressed more by the physical condition of these patients than by its association with a mentality different from the average. They describe an individual, usually a woman, presenting atrophied breasts undergoing cystic change; staining and pigmentation of the skin; hair turning grey and falling out; profuse offensive perspiration and a subnormal temperature; coldness and lividity of the extremities; wasting of subcutaneous fat and premature senility. The extreme cases Lane (376) described were so very few that they did not truly represent that large number of 'painful women' as Cabot (99) describes them. They complain of one or more varieties of pain situated in their 'midship section', which might be due to an organic lesion of one of the organs between the diaphragm and the floor of the pelvis, but is not. These have been more successfully pictured by Hutchinson (309). He describes the patient as more often a woman, generally a spinster, or else childless and in comfortable circumstances, who develops many varied and ever-renewed symptoms. They fall into two groups, one relating to the abdomen, while the other consists of symptoms more remote and general in character. These are described in great prolixity and in minute detail. Pain is very frequently complained of in the right iliac fossa or else a raw feeling inside. An indescribable sensation in the stomach and a dragging generally are also predominant symptoms. Constipation is more or less absolute and flatulence is frequent. General weakness or exhaustion is present, especially after a bowel action. Mental and physical torpor, inability to think, a poisoned feeling, and neuralgic pains all over are common. Headache and insomnia, undue susceptibility to cold, and constant catarrh in the throat complete the picture. While these descriptions portray the advanced stage of chronic intestinal invalidism they do not reveal the individual in the earlier stages of the complaint, such as he or she is when first seeking medical advice. Moreover, the earlier stages or milder degrees of the complaint do not show the extreme disproportion between the sexes which has been stressed by most writers on the subject. The patient comes complaining of digestive symptoms and general ill-health. Careful routine physical examination fails to reveal any abnormality, excepting poor nutrition and more or less obvious fatigue. Not infrequently an individual may

be stout, but, if so, is characteristically flabby. In most cases they are thin, looking and feeling ill, both mentally and physically. On inspection the individual, as a rule, presents the posture of fatigue, somewhat bent, with collapsed lower thorax and protuberant lower abdomen. The pupils are usually dilated, while the respiration is rapid and frequently irregular. The skin is likely to be dry, often rough, and usually of a 'muddy' colour. In the stout person the fat, instead of being firm and retained in position by the tissues, is soft and 'flows'. The muscles are small, of poor tone, and as lacking in resilience as is the subcutaneous tissue. Abdominal examination may be difficult at first on account of a strong spasm the moment the palpating hand touches the abdomen. With patience, the spasm will pass off to reveal a toneless musculature, through which it is easy to palpate the abdomen unless there is present generalized gaseous distension. If not, gurgling is constant in the region of the caecum and ascending colon, or in the left iliac region, from a distended sigmoid loop.

On the mental side, the most characteristic finding is a constant over-reaction to stimuli of all kinds. These patients are in a state of perpetual mental unrest, which is reflected in their changeability, lack of concentration, and difficulty in securing restful sleep. In women the manifestations of apprehension or suspicion may be displayed with frequent floods of tears. They complain of poor or capricious appetite, intermittent abdominal pains and flatulence, from which they find great difficulty in getting relief. Constipation is the rule. Finally the picture is completed by signs of vasomotor instability; excessive flushing of the face on the slightest provocation contrasting with its pallor in repose; tachycardia; cold and moist extremities; excessive sweating. In the very severe cases nervous energy has been wasted at such an abnormal rate that physical rest is enforced by a state of collapse, accompanied by nausea and vomiting.

Clinicians were not content with merely describing the condition; they naturally sought for an explanation on a pathological basis. The earlier attempts culminated in the classical work of Glénard; and in the succeeding sections I propose to review the different theories by dividing them into three main groups, namely, those which appeared before Glénard's work, Glénard's own theories, and those which have appeared after his influence has waned. This division is a very useful one, since his influence continued to the beginning of the present century, in the opening years of which new methods of investigation were introduced which revolutionized all previous concepts of the subject.

An Historical Outline of the Problem before Glénard.

The early anatomists regarded the abdominal viscera as possessing a definite unalterable form, and occupying a fixed position, any departure from which was presumed to be abnormal and duly recorded as such. Thus we find Franciscus de Pedemontanus (495) describing a dislocated kidney, and Riolan (517), not only recording a similar observation, but suggesting as a cause absorption of the perirenal fat. Both Riolan and Spigelius (570) observed, *post mortem*, localized

narrowings of the gut, 'agony contractures', which they suggested might occur during life, and by obstructing the passage of faeces produce what we would call to-day abdominal symptoms.

The works of Antonii de Haen (260–1) have several plates showing abnormalities of the hollow viscera. In Vol. x, Plate 1, is depicted a Lane's kink; in Plate 2 an undescended caecum; and in Plate 3 the transverse colon looping downwards below the umbilicus. In Vol. xi, Plate 3, there is an excellent picture of the hepatic flexure, showing what the French call 'canons de fusil'.

Lorenz Heister (271) in 1739 reported finding a liver dislocated into the abdomen.

Morgagni (465), a little later, describes no less than twenty autopsies in which he found the stomach and colon abnormally low. In Book III, Letter XXXIV, Sec. II (de intestini dolore), he says he has not mentioned anything like all the cases observed by him, and that they are far more common than is generally believed. He was the first to suggest that these deformities may be of congenital origin (Adv. anat. II, 14). In this view he was supported later by Fleischman (202), who in 1815 confirmed his observations. Annesley (24), on the contrary, believed that those abnormal positions were frequently due to an unusually long colon stretched by the weight of impacted faeces in constipated individuals. Esquirol (191), on the other hand, had noted abnormal positions of the hollow viscera as a frequent finding in autopsies on patients who had suffered from melancholia during life. He concluded that these were due to the general flabbiness of the tissues characteristic of melancholics.

In 1825 Matthew Baillie (31) was the first to report the palpation of a movable kidney in a healthy woman. A year later Aberle (3) published four autopsies where the kidney, palpable during life, was verified to be unduly mobile *post mortem*. He also noted in all four that the other abdominal viscera occupied an unusually low position. Girard (228) in 1837 distinguished between a movable kidney and a floating kidney, i.e., one completely surrounded by peritoneum forming a true mesentery. Rayer (507) increased our clinical knowledge of the subject by pointing out that movable kidney was commoner on the right side than on the left, commoner in men than in women, and usually found in association with hypochondriacal symptoms. He claimed that by holding the kidney in position with a suitable belt these symptoms might be relieved.

Cruveilhier (152) in 1849 gave a fairly precise account of the dislocation of the abdominal viscera, particularly of the transverse colon which, he says, may zigzag across the abdomen or else loop down *en masse* into the pelvis. Where this deformity is not due to traction by tumour or adhesions, he suggests the deforming effect of corsets on the liver as the cause, the descent of the intestine being secondary to the downward elongation of that organ. He also noted that in many cases an abnormally long transverse colon was really the result of the ascending and descending portions being unduly short.

Although in 1836 Rokitanski (524) had noted the association between

adhesions and bowel displacement, Virchow (606) was the first to elaborate a theory to explain it. He assumed a localized chronic peritonitis starting at the root of the mesentery in the region of the last lumbar vertebra and at the flexures. As the exudate organized, and the fibrous tissue contracted, various deformities and malpositions of the gut resulted. The cause of the local peritonitis was trauma from hardened faeces or, where the faeces were too fluid, from some chemical action. It may be noted in passing that Virchow completely abandoned this theory, and in 1890, according to Blad (66), wrote: 'In almost all adults partial states of dislocation of the viscera, and especially of the intestines, occur so frequently that more people have displacement than a normal location of the intestines.'

Engel (188) in 1860, discussing the influence of corsets on the thorax and abdomen, described various deformities which resulted from tight-lacing. He assumed that the liver, becoming elongated by the pressure of the corset, produced a downward dislocation of the hepatic flexure, ascending colon, and caecum. The transverse colon then formed a downward convex curve, which descended from the right crest of the ilium to reach the symphysis pubis, and from there ascended on the left side to 3–4 fingers' breadth above the crest, though never so high as in a healthy person. About the same time Frerichs (212) made similar observations, and did much to popularize the corset theory of visceroptosis.

In 1866 appeared the first monograph devoted solely to the dislocation of an organ, that of Rollet (526) on the kidney. In 1870 Chroback (126) suggested movable kidney as a cause of hysteria. With the appearance of Landau's (370–1) monograph in 1881 there started such a flood of literature on nephroptosis that by 1897 A. Macalister, in his article on Allbutt's (10) system (vol. iv, p. 350–1), was able to compile a carefully selected bibliography of 151 articles devoted to this condition alone.

Cantani (108) in 1866 reported a case where the whole liver was dislocated downwards and lying mobile in the abdomen. Ten years later Blet (67) collected ten cases from the literature, and a year after Wickham Legg (391) reported another twenty, along with a supposed case of his own. At the post-mortem, however, what was thought to be the liver proved to be a kidney tumour. This finding led Legg to doubt the existence of such a condition as hepatoptosis, since none of the reported cases had been confirmed *post mortem* In 1885 Landau (371) published a monograph on this condition which he assumed to be due to an unduly pendulous abdomen. This was quickly followed by that of Kuther (366). Landau also differentiated a virginal type of patient, excessively thin, from a maternal type excessively fat, in both of which the abdomen might be pendulous from muscular weakness. The latter type had been noted previously by Gueniot (257), who also recognized it as a cause of hepatoptosis (258).

Although both Riolan and Morgagni had noted that the spleen occasionally may be found dislocated, there is no further reference to it until Kuchenmeister's

description in 1856 (428). Clinically, a floating spleen is a somewhat rare condition, and Glénard (233) noted that it had only been found once in every 200 cases of visceroptosis seen by him. Its real importance lies in the fact that such a spleen is very liable to undergo torsion round its pedicle and produce the symptoms of an acute abdominal lesion. Hence most of the information regarding it has come from the surgeons, like Vulpius, who collected all the cases reported up to 1894, and Mayer (428) to 1899. Since torsion is a purely surgical condition, splenoptosis has never assumed much importance in the purely medical literature; hence it will not be referred to further.

As regards the stomach, it has been already mentioned that Morgagni noted its very low position in certain of his autopsies; but to Meckel (440) belongs the credit of observing that the stomach frequently occupies, especially in women, a vertical position instead of the classical horizontal one.

Klebs (351) gives a description of a case of gastroptosis, where the form of the stomach agrees with the hook-shaped form subsequently pointed out by Hertz (279) to be its normal shape. Kussmaul (365), who also noted these apparent abnormalities, was the first to attach clinical importance to them, and suggested that they were the cause of certain dyspeptic symptoms.

From this point onwards utter confusion seems to have involved the whole question of gastroptosis. Kuther and Dyer (364) in Germany, and Bouchard (76), G. See (550), and Mathieu (423–4) in France, who were investigating the motor function of the stomach by use of the stomach tube, started the confusion by assuming that a low position of necessity indicated atony and dilatation. It is only within recent years that the situation has been clarified by the aid of radiology.

In 1885 appeared Glénard's (229) communication to the Institute, in which, for the first time, it was suggested that this condition of prolapse of the abdominal viscera was intimately connected with certain local and general symptoms which had been previously described as separate clinical entities. To this hitherto badly-defined group of cases with dyspeptic and nervous symptoms he proposed giving the name enteroptosis. This name was chosen because he regarded the descent of the colon as the most prominent feature of the general prolapse, and it is always used by him as synonymous with visceroptosis. Since then the condition has been called by various names—Glénard's disease, visceroptosis, splanchnoptosis, &c.—and has aroused such widespread interest that by 1903 Blad (66) in his monograph refers to no fewer than 800 separate articles dealing with the subject. By 1912 Burckhardt (91) was able to collect several hundred more published in the interval. From this date onwards, judging by the lessened output of literature, interest in the condition, as such, has begun to wane, and excepting those of Dagna (156), Arlotta (26), and Ferrari (198) in Italy, Longyear (404) and Coffey (135) in America, and Knapps (355) in Germany, no recent monographs have appeared.

Glénard's Theories and those evolved under his Influence.

It is no easy task to give a brief outline of Glénard's enteroptosis theory. In some thirty more or less voluminous articles and monographs appearing between 1885 and 1899 Glénard advances from a purely mechanical conception of visceral displacements to a 'hepatism' theory, according to which these displacements are the result of functional changes in the liver. In his early work he assumes that the general health and digestion depend upon a state of mechanical equilibrium existing within the abdomen. The digestive tract, being about fifteen times as long as the distance from mouth to anus, must wind to accommodate itself to the abdominal cavity. At the points of winding, i. e. the flexures, the tract is more securely suspended from the posterior abdominal wall than elsewhere. These two facts readily explain how easy it is for normal function to be disturbed. Thus, for instance, if the contents of a loop of intestine be too much or too little in amount the flexures will be altered from their normal rounded form to an acute angle, which will form an obstacle to the passage onwards. Stasis will result, and the loaded bowel will now drag upon the flexures. The first to give way is the hepatic, since it is the most loosely attached of all. In descending it will pull upon the pyloric end of the stomach, obstructing that organ by the kink produced. As it descends further it will pull down with it the transverse colon, which in its turn obstructs the pylorus still more, so that the stomach now dilates. A series of kinks then develop, and a condition results in which we have a loop of bowel distended in the part proximal to, and contracted in the part distal to, each point of obstruction. Thus enterostenosis is added to enteroptosis. He assumed that the solid viscera are retained in position by the pressure of the gas-filled loops of intestine. When these undergo enterostenosis, the number of gas-filled loops become fewer and the solid viscera, now losing their chief means of support, drop. In his earlier work he makes it quite clear that the symptoms depend, not upon the position of the viscera, but upon the stasis resulting, exactly as Lane does at a later date.

From time to time Glénard gradually moved further away from this mechanical explanation. While at first regarding flaccidity of the abdominal walls as playing some part in the descent of the viscera, he subsequently denied it. Finally he came to regard the primary factor in enteroptosis to be a reduction in the intestinal volume brought about by perverted liver function. When the amount of gas in the alimentary canal lessens, the gut contracts and places itself against the posterior abdominal wall. The small intestines come to lie in the pelvis, the transverse colon passes across the abdomen below the umbilicus as a thin cord, the 'corde colique transverse', the sigmoid becomes palpable as a thin cord in the left iliac fossa, and the abdominal aorta can be felt pulsating as if it were immediately behind the anterior abdominal wall. He assumed that one of the functions of the liver is to regulate the gas content of the bowel through the coeliac plexus. Therefore, when the liver is functionally

deranged, it will produce the empty contracted condition of the bowel which leads to obstruction and ptosis. This functional derangement of the liver or 'hepatisme' may be hereditary or acquired. It may remain latent until toxaemia, infection, emotion, or trauma stirs it into activity. This theory, unsupported by a single pathological fact and based entirely on clinical observation, failed to gain many adherents outside France. But there it persists to this day, and in its present form is expressed by Monod (458) thus: 'By hepatism is meant a diathesis, hereditary or acquired, characterized by inadequacy of the liver cells. A vicious circle is thus created, since the poisons which are no longer detoxicated by the liver react in turn on its cells. Disturbance of the intra-hepatic circulation follows, and in sequence to this there arises a like disturbance in the circulation of the bowel. The subsequent effects observed are a diminution in the muscular tonicity of the gut and a lowering of the intra-abdominal pressure. Reduction in the lumen of the intestines then takes place, followed by enteroptosis, beginning at the hepatic flexure.' While Glénard's theories failed to win many supporters, the wealth and accuracy of his clinical observations compelled attention. Krez (364) and Ewald (192) in Germany, with Debove (164), Montennuis (459), and Mathieu (425) in France, early recognized their importance. A few years later, Lund (405), Einhorn (184), Meinert (441), and Dole (168) recognized the condition in America, but it was not until 1896 that Treves (593) wrote the first paper in England on the subject, followed by Gardner (217) and Bruce Clark (129) in the same year. They, along with Tuffier (596) in France, assumed that in these cases there existed a constitutional congenital weakness of the tissues of both abdominal wall and mesenteries. These stretched under strains and stresses ineffective in a normal individual. Stiller (573–4) elaborated the constitutional aspect of the condition, suggesting a congenital weakness, both physical and psychical, whose stigma was a floating 10th rib which he claimed to be present in all his cases.

Obrastow (485) by percussion and palpation noted a relationship between body build and the position of the stomach, observing that normally it tended to lie much lower in long thin individuals than in short broad ones. He regarded the loss of tone in the abdominal muscles, the loss of peritoneal fat, and an associated state of neurasthenia as the cause of the symptoms, and not the low position of the abdominal viscera. As the result of continued observation, Mathieu (427) also came to disagree with Glénard, and pointed out that the symptoms of enteroptosis might be met with in individuals who showed none of the changes in the abdomen supposed to be pathognomonic, and, moreover, that in many of them the abdominal wall appeared quite firm.

This led to a revival of the 'corset theory' at the hands of Chapotot (120), Hayem (270), and others. These writers suggested that the pressure of the corset might produce severe visceral dislocations even in the presence of a firm abdominal wall. Fuchs (216) and others, however, showed that visceral dislocations might be found in young women who had never worn corsets. None the less, the majority of writers on the subject continued to regard weakness of

the abdominal wall as the chief factor in the production of ptosis, and they sought some other explanation of this weakness where it could not be shown to have resulted from repeated pregnancies, ascites, or any other definite known cause. Thus Schwerdt (546–7) held that in many cases it resulted from a disturbance in the innervation of the abdominal muscles. Wolkow and Delitzen (639) agreed with him. They claimed to show that the abdominal wall regulated the intra-abdominal pressure, and that only when the latter fell below a certain point did the viscera drop and symptoms arise. Yet ten years previously Weisker (618–19) had demonstrated that the intra-abdominal pressure, in the sense of a retentive force, is insignificant. Several years had yet to elapse before it was conclusively demonstrated that the intra-abdominal pressure is negative, and not positive, and that the abdominal wall plays no part in retaining the viscera in position.

Rosengart (529) suggested that the condition was really a reversion to the foetal type, and Kraus (361) concluded that this was due to a failure of the thorax to undergo full development. He had noted the clinical condition in individuals whose abdominal walls appeared to be perfectly well developed, but whose thorax, being abnormally long and narrow, did not allow the viscera to ascend normally into the upper abdomen.

Keith (339), also struck by the form of the thorax in these cases, published a theory which he has little modified in the course of years. He regards Glénard's disease as essentially due to a vitiated method of respiration. The viscera in the upper segment of the abdomen covered by the diaphragm acts as a piston. On inspiration the diaphragm pushes this piston downwards and forwards; on expiration the abdominal muscles push it upwards and backwards. At all stages of respiration this piston is delicately poised, and the ebb and flow are so finely adjusted that the slightest disturbance in the mechanism of respiration will result in a displacement of the organs forming the piston. This displacement will then pull or push the hollow viscera out of position. Latterly (343) he has somewhat modified this view, and has come to regard the transversalis muscle as the most important factor in regulating the piston action and in holding the viscera in position. He supposes that when we assume the erect posture the viscera drag on numerous Paccician-like corpuscles at the roots of the mesenteries. This stimulus initiates a reflex mechanism which throws the transversalis into contraction to 'gird our loins'. He suggests that through faulty feeding and unhygienic living this mechanism breaks down and the unsupported viscera then drop.

The last theory to be mentioned in this section, though elaborated after the introduction of X-rays, is a logical continuation of the above, and so will be considered here. It is that of Agnes Vietor (600–3), who believes the fundamental cause of visceroptosis to be an abdominal incompetence from a failure in normal development. This displays itself not only in the shape and size of the abdominal cavity, but also by a defective visceral fixation. The most constant departure from the normal is a retracted lower thorax. She claims to show that

the developmental evolution of the human type is not completed at birth, and that variations in these developmental processes may be observed progressing throughout life. These processes may reach normality, may be retarded, uncompleted, or undergo reversion, and thus produce varying grades of visceroptosis.

Cameron (101), however, working on similar material, has shown that the relations and positions of the various abdominal viscera are fixed at the end of the third month of intra-uterine life, and that no further alterations occur, except in the position of stomach and caecum which remain essentially mobile organs throughout life.

In 1898 Boas and Levy Dorn (72) for the first time employed the opaque meal in the radiological investigation of the gastro-intestinal tract in man. By 1900 its use had become universal, and the lessons learnt from it have rendered the majority of these hypotheses no longer tenable.

Theories which have appeared since the Introduction of the Röntgen Rays.

The present century has contributed to the study of visceroptosis along three main lines—radiological, anthropological, and surgical. The first two have borrowed so extensively from each other that it is preferable to discuss them together. On the other hand, the surgical contributions require separate consideration, since the surgeon, while not disdaining the aid of radiology, has in the main preferred to be guided by his own operative findings.

1. *Theories based on radiological and anthropological evidence.* The opaque meal for the first time enabled the living stomach to be visualized by the Röntgen rays. The picture presented differed so widely from the conception obtained by inflation and percussion that radiologists were in doubt at first which to accept as representing the truth. It had been assumed that the detection by percussion of the greater curvature below the umbilicus was indicative of gastroptosis, gastrectasia, or both combined. This state of affairs, in which the body of the stomach lay below the pyloric opening, was supposed seriously to handicap the evacuation of its contents, since it was assumed that they depended largely on the influence of gravity for their removal. As early as 1896 Duret (180) had suggested an operation for shortening the lengthened stomach to permit it again to empty by gravity. From this year onwards gastropexy became a favourite operation with many continental surgeons, especially Rovsing (532), who attributed all the symptoms of visceroptosis to the stomach's inability to empty. He assumed the chronic state of malnutrition observed in these cases to be due literally to starvation, since the residue constantly present in the stomach prevented an intake sufficient to maintain nutrition.

The radiologist's first observation was that in the vast majority of healthy stomachs the greater curvature extended below the umbilicus, and they had to seek for a fresh definition of gastroptosis. Thus Holzknecht (285) in 1906 considered gastroptosis to exist when the pylorus was not the lowest point of the stomach. Schlesinger (541–2) regarded lengthening of the gastric wall, drawing

down of the cardia and upper pole of stomach, and sinking and rolling up of the pylorus as indicative of its presence. Beclere and Meriel (56), however, pointed out that the stomach never leaves its attachment to the diaphragm, and preferred to speak of a lengthened stomach rather than a ptosed stomach. They distinguished two kinds, one with normal tone and tubular in form, the other atonic, with an expanded lower pole, and tending to show delayed motility.

Kaestle (327) regarded a high pylorus with a low greater curvature as the chief indication of gastroptosis. On the other hand, Groedel (252–3) assumed the low position of the pylorus to be the most important sign. As late as 1915 Hurst (299) defined complete gastroptosis as follows: 'When the stomach is not only abnormally low in the erect position, but the greater curvature reaches below the umbilicus in the horizontal position.' At the same time it was observed that the normal adult's stomach takes one of two general forms, the cowhorn and the fish hook. The fish hook was found to be by far the most common form. It resembles a hook or J, descends more or less vertically from the diaphragm, curves across the spine and ascends to the pylorus which lies above the level of the lowest point of the lesser curvature. The much rarer cowhorn is a relatively small stomach, broadest at the fundus and narrowing progressively to the pylorus, which is its most dependent portion. It occupies an oblique, sometimes almost transverse, position, and lies well above the umbilicus.

The physiologists, led by Cannon (107), utilized the X-rays to investigate the motor mechanism of the stomach, and they showed that it empties by a series of definite muscular contractions which render it independent of the action of gravity. Schlesinger (542), appreciating the importance of muscle integrity, introduced his well-known classification of the stomach according to the state of tone of the muscle, the orthotonic, hypertonic, hypotonic, and atonic; the former two being normal, and the latter two pathological variations. Stiller (575), Bartel (44), and others attempted to co-ordinate these confusing findings. They noted that there was an apparent relationship between the body build of the individual and the position, tone, and motility of the stomach. In individuals with slight skeleton, long narrow sunken thorax, steeply falling ribs, wide intercostal spaces, and acute epigastric angle, the stomach tended to be low and vertical with diminished tone and motility. On the other hand, in robust individuals with broad short deep thorax and obtuse epigastric angle, the stomach tended to be cowhorn in shape, small, lying transversely, hypertonic and hypermotile. Stiller (576) also showed that, not only was a low atonic stomach a common finding in a flat abdomen, but that even the high hypertonic form was equally frequent in individuals with flaccid pendulous abdomens.

Manouvrier (416) and Godin (235) had shown that the races of Europe could be divided into two extreme types which they called Brachyskele and Macroskele corresponding with the clinical types termed asthenic and apoplectic, or sthenic by Stiller. They also identified an intermediate type, the Metaskele.

Treves (592), many years previously, from a study of 200 species of animals,

had shown that the length of the intestinal canal depends on food and environment, and suggested dividing the human race into two types, the carnivorous with short intestines, and the herbivorous with long. Bryant (83), in America, combining the observations of Treves, Manouvrier, and others, confirmed the existence of these two extreme types, and pointed out more than one hundred points in which the carnivorous differed from the herbivorous. Stockard (577–9) preferred to call them the lateral and the linear types, and noted that races living along the coast tend to be linear, while those in the interior tended to be lateral. He suggested the linear type was a fast growing, high metabolizing, thin, but not necessarily tall group, while the lateral was slower in maturing, stocky, and rounder in form. Bean (50–3), preferring to call them meso-ontomorph and hyper-ontomorphs, differentiates them by the following characteristics:

Meso-ontomorphs.	*Hyper-ontomorphs.*
Face. Large, round, or square. Large prominent cheek-bones. Broad jaws.	Large and narrow; high forehead; pointed chin.
Cranium. Round or boxed, broad and short.	Long and narrow, prominent behind, straight and high in front.
Cephalic. Index 80 and over.	75 and under.
Trunk. Broad, short; shoulders sloping.	Long and narrow; shoulders erect.
Extremities. Short, stocky.	Long and slender.
Sitting height. 53·5 cm. or more (relative to stature).	52·5 cm. or less.
Stature. 165 cm. or less.	About 175 cm. or more.
Teeth. Large, sound, retarded in growth. Dental arch broad.	Small, ill-formed, irregular, crowded, and appear early. Arch long, high, and narrow.
Lungs. Broad and short.	Long and narrow.
Heart. Large.	Small.
Stomach. Large, transverse.	Small, almost vertical; on left side.
Liver. Large, 1500–2000 grm. lies transversely.	1000–1500 grm. and lies to right of sagittal plane.
Kidneys. Large.	Small.
Small intestine. 20–30 ft. long and sluggish. Needs food of great bulk and little nourishment. If excessive in quantity, patient becomes plethoric and then kidney disease develops.	10–20 ft. long and active. Needs food readily digestible concentrated as milk, eggs, and meat.
Susceptible to diseases of tissues derived from mesoderm, e. g. kidney, heart, joint, muscle, &c.	Susceptible to diseases of tissues derived from ecto- and endoderm, e. g. skin, alimentary tract, and nervous system. Tuberculosis, cancer, pellagra, leprosy, and all diseases of chronic form that come from deficient nourishment.
Mental. Slow, sure, methodical, practical, painstaking, comprehensive, well balanced, judicious.	Quick, active, vivacious, imaginative, inventive, unstable, idealistic, executive.
Thyroid type. Intermediate.	High thyroid type.

These observations stimulated radiological research into the position of the hollow viscera in unselected individuals free from all digestive symptoms.

Mills (451–3) and Ansell (25) in America were the pioneers in this investigation, but were to a certain extent influenced by the preconceived idea that each individual could be fitted into a definite type. Assuming the existence of these types, Mills, from a radiologist's standpoint, classified them as follows:

Hypersthenic. In this type the stomach is cowhorn in shape, lies high and transversely, and shows active peristalsis, emptying in 3–3½ hours. The small

intestines lie above the pelvis, and the caecum is well up in the right iliac ossa. The flexures are attached high with the transverse colon crossing the abdomen above the umbilicus. The haustra are small and numerous. The descending colon sweeps straight down to the pelvis with a short sigmoid loop. The colonic residue after 24 hours, if any, is small.

The sthenic shows much the same characteristics with slightly lower position and slightly greater residue.

Hyposthenic. This is characterized by the J-shape stomach in an individual with a body build somewhat below the average. The lesser curvature extends below the inter-iliac crest. The pylorus is low, usually in the region of the umbilicus, and the fundus is in the left iliac fossa. Peristalsis is not so active and the stomach usually requires 5–6 hours to empty. The small intestine and caecum are both in the pelvis with the transverse colon resting on them.

Asthenic. All the characteristics of the hyposthenic are exaggerated. The stomach is dilated and its greater curvature lies in the pelvis. Tone is poor, peristalsis inactive, and emptying time rarely under 6 hours. The colon tends to be spastic, with a 48 hours' residue. In a thousand individuals examined by him, Mills (451) found the following distribution:

	Males.	Females.
	%	%
Hypersthenic	89·4	10·6
Sthenic	59·9	40·1
Hyposthenic	40·4	59·6
Asthenic	20·3	79·7

He then examined 2,500 individuals complaining of digestive symptoms and found the distribution of types as follows:

	%
Hypersthenic	3·6
Sthenics	44·7
Hyposthenics	37·8
Asthenic	13·9

These figures show that the distribution of the types in the group with symptoms is practically the same as in the population at large. This suggests, therefore, that there is no causal relationship between low atonic viscera and the production of symptoms. Mills (452) made a further observation of considerable importance. He noted that the head of the bismuth column reached the various landmarks in the gastro-intestinal tract at approximately the same time in all, irrespective of the position of the viscera and the tone of the gut, and in this respect, there was no difference between individuals who had no residue after 24 hours, and those with a residue after 72 hours. Bryant, desirous of checking the generally accepted data concerning the position of the abdominal viscera in the cadaver, carefully examined *post mortem* 177 males and 113 females. In 48 per cent. he found wide departures from the generally assigned normal positions. The widest departures from these positions were found to occur in the ascending colon, ileocaecal valve, caecum, hepatic flexure, and liver in that order of frequency. Although the stomach and right kidney did not show such

extreme variations, they equally frequently departed from the position stated to be normal.

The most careful work, and work uninfluenced by any preconceived theories, was that done by Moody, Nan Nuys, and Chamberlain (461–2). They picked out 600 of the healthiest students they could find at the University of California of whom 200 were athletes or qualifying in physical culture. None had ever complained of dyspeptic symptoms. In the standing position it was found that the lowest portion of the greater curvature of the stomach dropped below the inter-iliac line, i.e. a line drawn between the highest points on the iliac crests, in 74 per cent. of the men and 87 per cent. of the women. In 25 per cent. of the men and in 46 per cent. of the women, it was more than 10 cm. below. They concluded that the greater curvature of the normal stomach may be found at any point between 7·3 cm. above and 13·7 cm. below the inter-iliac line. Even the lesser curvature in the antral region was found below the inter-iliac line in 13·1 per cent. of the men and 28·8 per cent. of the women, and in some cases the pylorus was below the line. In a subsequent paper (462) they continued the investigation with a view to comparing the erect and recumbent positions. They found the excursion of the stomach, i. e. its difference in position in the recumbent and erect posture, greater in females than in males. That is to say, whereas in the erect position the stomach in women tends to be lower than in men, yet in the recumbent posture it tends to occupy the same position as in men. The colon, on the other hand, not only lay lower in women than in men, but remained low in the recumbent posture. They found that the pylorus and liver normally have a considerable excursion. As regards the pylorus, it may be anywhere between the upper border of the first lumbar vertebra and 5 cm. below the inter-iliac line. In 69 per cent. of both sexes it was below the transpyloric plane, and in 5 per cent. it was in the pelvic cavity, and in 13 per cent. it lay to the left of the sagittal axis. They also concluded that the normal position of the caecum is in the true pelvis.

Moody (460) continued their work at the University College, London. From a study of 100 women and 50 men he found the stomach lay lower in British than in American students, the greater curvature being below the inter-iliac line in 87 per cent. men and 96 per cent. women. In 44 boys of between 7–14 it was below in 84·2 per cent. By allowing the individual to take one swallow of the barium meal and marking on the abdomen with a penny the lowest point of the shadow, he was able to map out the position of the greater curvature of the empty stomach. This he found to be below the inter-iliac line in 50 per cent. men, 52·3 per cent. boys, and 70 per cent. women.

The distance through which the lowest part of the greater curvature was moved down by the barium meal (1½ lb.) varied from a small fraction of an inch to four inches.

He then investigated 50 women and 50 men of ages between 40–81 years and all complaining of digestive symptoms. He found the lowest part of the greater curvature below the inter-iliac line in 82 per cent. males and 88 per cent.

females. From this it follows that low stomach occurs more frequently in healthy young adults than in elderly individuals with dyspeptic symptoms. He came to the following conclusions:

(1) Long stomachs, with the lowest part of the greater curvature 6 in., the lowest part of lesser curvature 3 in., and pylorus 2 in. below the inter-iliac line are normal.

(2) Transverse colons dipping into the true pelvis are normal.

(3) Caeca with the blind end low in the true pelvis are normal.

(4) Livers with the lower border 1 in. or more below the inter-iliac line are normal.

(5) The ability of the stomach, colon, and caecum to function normally is independent of their position.

Faber (195) in Scandinavia, and Campbell, and Conybeare (106) in England came to similar conclusions.

The only constant relationship between build and position these observers could find was that since narrow long thoracic cavities tend to be associated with narrow short abdominal cavities, a stomach will appear low in such an abdomen. Hrdlicka (289) has shown that the average American has a shorter thorax and longer abdomen than the average Briton, which explains Moody's finding that the stomach is apparently lower in British than in Americans.

Barclay (42) some years ago pointed out that tone is an automatic contraction of the stomach musculature, which compensates and counteracts the effects of gravity by holding up the food in tubular form. The tone is independent both of the position of the stomach and its peristaltic activity. He regarded atony as a 'defective physiological action rather than a pathological condition'.

This concept seems to have led Hurst to a repudiation of his previously held views on the subject of gastroptosis. In a recent article (307) he comes to the conclusion that the types of stomach commonly diagnosed by radiologists as hypertonic and dropped, are quite incorrectly named. Experiments with stomach tubes connected with a manometer and the more recent radiologic investigations have shown that the tone of the normal stomach adapts itself to the volume of its contents and that the pressure within remains constant. This is shown by the fact that the upper level of the contents are found just under the diaphragm whether the stomach lies horizontally above the inter-iliac line, or vertically with the greater curvature in the true pelvis. Yet in the past the horizontal stomach was said to be hypertonic and the vertical one 'dropped'. Hypertonic is obviously a wrong term since the tone is the same in the two stomachs. Gastroptosis is equally wrong since it should indicate that the stomach has fallen. It is true that in so-called gastroptosis the stomach falls on standing from the position it occupies when lying; but every stomach does this and there is no evidence that it has fallen from a higher position than it once occupied in the erect position. So-called gastroptosis is quite common in people with excellent

abdominal muscles who have been always thin; it also occurs, though less frequently, in stout individuals.

On the other hand, the so-called hypertonic stomach may exist in people who have lost weight and whose abdominal muscles have become very weak. Nothing in fact will make such a stomach drop materially, just as nothing will make the so-called dropped stomach rise to the level of the average stomachs.

The only satisfactory explanation is to regard the difference between the two types of stomach as due to anatomic variations from the average normal length. The stomach swings freely between two fixed points. These are, where the oesophagus passes through and is fixed to the diaphragm about one inch above the cardia, and the point where the duodenal bulb joins the descending retroperitoneal portion of the duodenum. If it is short, it assumes the diagonal or almost horizontal position of the so-called hypertonic stomach; if it is long, it assumes a vertical position with a steeply ascending pyloric part giving the appearance of the so-called dropped stomach. The 'orthotonic' stomach is simply a stomach of average length.

Hurst goes further and states that a 'hypotonic stomach' corresponding with the 'atonic dilatation of the stomach' of pre-radiologic days does exist. In most cases it has quite a different form from what is commonly described. It is rare and never of any clinical significance, being found incidentally in routine radiologic examination when it reveals itself by the upper level of the gastric contents being lower than usual without any corresponding excess of gas being present in the fundus. He agrees with Barclay that tone is completely independent of peristalsis, and that atony does not result in any delay in evacuation, or give rise to symptoms, except as a complication of pyloric obstruction of organic origin.

It is now agreed that there is no relation between the strength of the abdominal muscles, amount of subperitoneal fat, and the position of the stomach. Chamberlain (461) observed an athlete who trained himself until he could sit up from the reclining position 300 times in succession without resting, and failed to find any upward move of the greater curvature of the stomach result from this abdominal muscle development. Independently Mills, Carman, Campbell, and Conybeare came to similar conclusions.

Finally, Mackeith, Spurrell, and Warner (409) have recently reported the case of a boy of 15 with a congenital deficiency of the anterior abdominal muscles in whom they found the stomach normal in tone, if anything rather higher than normal and with no greater excursion. We now know that there is a negative pressure within the abdomen, as can be observed from the rush of air on every occasion when the abdomen is opened with the patient in the Trendelenburgh position. The state of affairs within the abdomen is much like that of a hot-water bottle which has some water but no air in it. When this bottle is hung up by its neck the water remains a vertical column which reaches up to the plug. However, as soon as some air is let in the water falls to the bottom of the bag.

The condition of the pelvic floor is probably more important than the abdominal wall in deciding whether the column of viscera floating on the top of one another is a long or short one, but probably neither have any influence on the exact relationship of the viscera to each other. Recent work by Wagoner (608) shows that any permanent increase in the intra-abdominal pressure, or rather reduction in the normal negative pressure, is fatal to experimental animals, a finding distinctly at variance with the widely held belief that beneficial results from treatment in cases of visceroptosis is due to a raising of this pressure. For instance, in a comparatively recent review of gastroptosis by Seale, Harris and Chapman (264), after discarding most of the previously held theories on the subject, still hold that the solution of the problem of gastroptosis is not to treat the stomach or try and alter its position, but to increase the intra-abdominal pressure.

Conran (141), however, may be regarded as having given the *coup de grâce* to gastroptosis on the clinical side. He found that a low stomach may be unaccompanied by any symptoms which could reasonably be attributed to it. Where symptoms are complained of, they vary greatly and are not in accordance with the physical signs discovered.

In conclusion, reference must be made to a condition which has been the centre of much interest and of no little controversy during the six years which have elapsed since Kellog (346) and Wilkie (632–3) first described it under the heading of chronic duodenal ileus. By this is meant, the production of vague digestive symptoms from intermittent compression of the third part of the duodenum at its junction with the fourth part. Wilkie holds that any factor which allows of an undue drag upon the mesentery may induce it from pressure by the superior mesenteric vessels on the duodenum. He cites as causes: congenital or acquired visceroptosis allowing the small intestines to sink into the true pelvis, sagging of the proximal colon, loss of supporting fat, and defective bodily posture. We have seen there is very little evidence for the belief that in the intact abdomen the viscera ever drag on the mesenteries. According to Keith (343) the function of the mesentery is limitation of movement and not support, a function compatible with Alvarez' (20) observation that the viscera 'float' in the abdomen. Hurst's (307) view seems more in accordance with the evidence. He holds that symptoms can only occur from the natural drop of the stomach on adopting the erect posture when the peritoneal covering of the descending part of the duodenum is so taut as not to allow the whole duodenum to drop on standing. In most individuals the junction between the duodenal bulb and descending duodenum drops with the rest of the stomach. In exceptional cases it does not, and a kink results which produces more or less severe gastric stasis. The condition is then analogous to the rare cases of nephroptosis in which an aberrant vessel leads to Dietl's crisis. Apart from that, a low stomach and a low kidney are equally common and equally unimportant, whilst a kinked ureter and a kinked duodenum are about equally rare.

2. *Theories based on surgical observation.* Priority must be given to Lane's views on account of the long period over which he has been advocating them, and the widespread influence they have exerted on medical and surgical practice. As long ago as 1885, Lane (373) observed a band on the under surface of the mesentery at the junction of the iliac and pelvic segments of the colon firmly securing the bowel to the iliac fossa. This band caused a certain degree of angulation and rotation of the gut, and appeared to diminish the lumen sufficiently to offer an obstruction to the passage onwards of its contents. With this observation as a starting-point, Lane in the course of years elaborated a theory which, in its present form, may be stated thus. The gastric intestinal tract is a drainage system, at certain points of which exist structures to regulate the onflow and prevent the backflow of the intestinal contents. These structures or sphincters are found at the lower end of the oesophagus, at the pylorus, and at the junction of the pelvic colon with the rectum; subsidiary ones occur in the second part of the duodenum, at the lower end of the ileum, and in the transverse colon. Each of these regulates the rate of flow of the intestinal contents into the segment below and prevents their return into the segment above.

On account of the unnatural diet of civilized man the rectum is not stimulated to empty itself more often than once a day. This produces overloading of the pelvic colon. The erect posture of man allows this overloaded portion of the gut to drop, producing a kink at the junction of the pelvic and iliac segments. This kink delays the passage onwards of the contents of all parts of the gut proximal to it as far back as the stomach itself. One of two things may result from this delayed passage of the intestinal contents according to the vitality and resisting power of the individual. In those with minimum vitality, little attempt is made to oppose the increasing bulk and weight of the intestinal contents, the sphincters cease to function, and the various segments of the gut dilate, elongate, and become tortuous. First the pelvic colon, descending and transverse colon, then the ascending colon and caecum, and finally, the small intestine take part in this process. The dropped intestines now drag upon the fixed duodenal-jejunal junction, narrowing and obstructing it, which leads to distension of the first part of the duodenum. This distension in turn produces pyloric spasm, which brings about gastric stasis, followed by dilatation and dropping of the stomach. In this way complete visceroptosis results. Secondary changes now occur. The mucous membrane of the prolapsed intestine becomes damaged and permits the absorption of poisonous products from the putrefactive process which the delayed intestinal contents undergo. These poisons enfeeble the muscular coat of the bowel still more, leading to greater and greater absorption and ever-increasing delay. On the other hand, in individuals of greater vitality, the new formation of bands and membranes in the mesentery takes place in an attempt to support the loaded sagging gut. Unfortunately these bands contract, and in doing so distort and angulate the bowel, producing in time a well defined obstruction which leads to symptoms of a local and mechanical character quite different from the general symptoms met with in the visceroptotic. Some of Lane's followers,

while agreeing with him in the main, propose slight variations in the genesis of the condition. Thus Jordan (326) regards artificial feeding in infancy as the chief cause. According to him, artificial food causes the caecal contents to be solid instead of fluid. This gives rise to sacculations which cause the caecum to lose some of its propulsive efficiency. The caecum now dilates, and in so doing produces a spasm of the ileo-caecal valve. The terminal coil of the ileum hypertrophies to overcome this spasm, then dilates, and the now over-distended loop droops into the pelvis, thus initiating the ptotic process.

While Lane was elaborating his theory in England, the orthopaedic surgeons in America, led by Martin (419), Smith (565–6), and Goldthwait (236–8) evolved a totally different concept. Impressed by the anthropological grouping of individuals into types, the school of Goldthwait, as it may be called, postulated the existence of a certain body build which alone could be called normal, and regarded the different types of the anthropologists as pathological deviations from it. Classifying the build of individuals into normal, broad back, narrow back, and mixed, Goldthwait identified his narrow back with the enteroptotic habitus of Stiller. In this type, on account of the narrow thorax, the expansion of the lungs is poor, and the aeration deficient, causing stagnation in the pulmonary circulation which is accentuated in turn by the small cramped heart found in association with it. As a result, the blood-pressure is low and the blood poorly oxygenated. In an effort to correct this state of affairs, the right side of the heart hypertrophies and causes distension in the pulmonary vessels which now press on the lymphatics. This pressure on the lymphatics is said in some way to favour invasion of the lung by the tubercle bacillus. Owing to the narrow upper abdomen all the abdominal viscera lie low; since the lowest part of the stomach is lower than the pylorus the stomach contents cannot easily empty and gastric stasis results.

The intestines, being loosely attached, are readily kinked and, being shorter than usual, are not efficient assimilative organs. Kinking of the intestine, besides delaying the onward passage of the contents, produces a drag on the solar plexus, so that a double effect is produced. That is to say, symptoms of auto-intoxication arise from stasis, and those of neurasthenia result from the drag on the solar plexus. The basic assumption of this school is that the abdominal viscera depend for their support upon a correct posture whose action is explained as follows. When an individual holds himself correctly the diaphragm is high and the abdominal wall flat, so that the stomach is tucked well up into the arch of the diaphragm and kept there through the vacuum created by its high dome formation; at the level of the last lumbar vertebra the antero-posterior diameter of the abdominal cavity is only about a third of the maximum antero-posterior diameter of the body, so that the small intestines are largely held up in the upper part of the abdomen by the shelf thus formed. These in turn give support to the transverse colon and the stomach. The axis of the abdominal cavity inclines upwards and backwards to such a degree that the kidneys and spleen have definite support from the posterior abdominal wall. Any posture which

alters the body axis removes this support from the kidneys and spleen, and abolishes the shelf on which the small intestines partially rest. Then, by the action of gravity, the abdominal viscera descend *en masse* into the lower abdomen. According to Moore and Wheatley (463) if the child is trained to maintain a correct posture from early life, wears no constricting garment round the lower thorax, nor excessively heavy ones from the shoulders, visceroptosis would not and could not develop. Strauch (584) and Knapps (355) in Germany, Dagna (156) and Arlotta (26) in Italy, and Cochrane (132) in Scotland, are attempting to spread this purely mechanical conception of disease beyond its native Boston. It has few, if any, adherents among English orthopaedic surgeons who find this simple mechanical interpretation quite inconsistent with clinical observation. They prefer to regard posture and symptoms, not as cause and effect, but as expressions of a common underlying cause.

This view is well expressed by Bankart (34), who says 'postural deformity originates as a functional nervous disorder and the cause is to be sought in the mental rather than the physical condition of the patient. There is frequent association of postural deformity with neurasthenia and with a neuropathic family history.'

While Lane and Goldthwait were seeking an explanation which would cover all the diverse phenomena of this condition, other surgeons were so obsessed by the apparent local nature of the symptoms that they felt a strictly localized pathology must account for all the other symptoms, no matter how general and remote.

Chronic appendicitis. As far back as 1896 Rutherford Morison (466) had suggested a chronic inflammation of the appendix as the cause of indefinite long standing, right-sided abdominal pain, for which Ewald (194) coined the term appendicitis 'larvata'. The success of Beclere (55) in visualizing the appendix by X-ray, and of Grigoryeff (250) in showing that the appendix can only be seen if the lumen is sufficiently patent to admit the opaque material, stimulated greatly the investigation of chronic appendicitis by radiologists as well as surgeons.

Graham and Guthrie (242) in America, Paterson (490) and Fenwick (197) in England became its foremost exponents as a cause of vague dyspeptic and abdominal symptoms of long duration.

In 1910 Moynihan (472) coined the term appendix dyspepsia to denote this type of case, and three years later (473) went so far as to say that 'in the majority of cases where the symptoms would justify or compel a diagnosis of gastric ulcer, the patient is really suffering from a lesion, more often than not, in the appendix.' By now the wave of appendectomy was at its height, and when the appendix removed appeared normal to the naked eye, surgeons found confirmation of their diagnosis in certain microscopic changes which seemed to be departures from the assumed normal appearance. Aschoff (28) initiated the pathologists' protest against regarding many of these changes as pathological, by pointing out that the natural obliterative process, which all appendices undergo after 10 years of age, like lymphoid tissue elsewhere, had been mistaken for a pathological one.

On the clinical side Dieulafoy (166) in France, had already insisted upon the fallacy of attributing every obscure pain in the right iliac fossa to the appendix. Later, Hawkins (267) showed that simple caecal spasm might mimic chronic appendicitis.

Among the surgeons Morris (469) was one of the first to admit that the removal of the appendix failed to cure symptoms when its pathology was of the types he called irritans and syncongestive, the two commonly met with in neurasthenic and enteroptotic individuals.

Williams and Slater (634) confirmed Aschoff's findings, and Liek (403) found that only 100 out of 1,000 appendices removed showed signs of true chronic inflammation. Gibson (222–3) reported, that of 446 cases operated upon for chronic appendicitis 103 were quite unrelieved, and 65 only partially so. Lichty (401), in 517 consecutive cases, found 243 quite unrelieved. Yet the majority of surgeons were still unconvinced and pointed to Rosenow's (530–1) work on the specificity of streptococci from teeth, tonsils, and appendix in support of their views.

Even physicians like Hurst (303) claimed that they had seen ileal stasis, hour-glass contraction of the stomach, &c. produced by pressure over the so-called chronically inflamed appendix. In explaining the failure of appendectomy to remove symptoms they recalled Rosenow's teaching, that removal of the appendix alone was not sufficient, since it had become infected from a primary focus in the teeth and tonsils, which also required removal for a complete cure.

De Martel and Antoine (417) analysed a series of 124 cases clinically diagnosed as chronic appendicitis, and found at operation that only 34 appeared to have a lesion in the appendix itself. The others showed the following conditions: in 17 cases, undue mobility of the whole caeco-colon; in 14 a fixed low caecum; in 10 a fixed high caecum; in another 10 the hepatic flexure in a state of 'canons de fusil'. The remaining 39 showed a diversity of appearances such as mobile caecum, Jackson's membrane, Lane's kink, simple cecalgia, simple spasm, &c.

Cabot (100) in analysing the case records of 15,000 cases in which dyspeptic symptoms had been the chief complaint, found that although in no less than 12,600 were they attributable to lesions outside the stomach itself, in none were they due to chronic appendicitis. Blackford (65) in an analysis of 1,000 cases with digestive symptoms and abdominal pain reported that in 25 per cent. no recognizable lesion was detected and a further 6 per cent. could not be classified. He found that of 130 cases who had the appendix removed, 70 were no better than before the operation. In a second series of 1,000 cases, 202 had previous laparotomies with 131 appendectomies. Of the appendectomy cases, 85 were unrelieved. He concludes that the appendix is held accountable for stomach disturbances far more frequently than operative results justify. Whiteford's (629) contention that the diagnosis of chronic inflammation of the appendix as a condition requiring operation should be abandoned, is supported by the experience of Deaver (162), Bettman (61), Eastman (182), Held (273), and other surgeons. The most recent attempt to explain the pathology of these cases is that of Holder

and Menninger (283), who claim to find in 98 per cent. of the microscopically normal appendices some mechanical abnormality, congenital or acquired, which by interference with the blood supply, produces symptoms. However, Orndoff (486) who has examined the appendix radiologically by a new technique, finds that unless the appendix is fixed along its entire length it is not mechanically the cause of symptoms, no matter what its position, shape, or structure may be. It is not denied that a true 'chronic' appendicitis does exist, but its symptomatology is quite different from the condition here discussed. Recurrent attacks of acute or subacute appendicitis with latent symptomless intervals between should alone be referred to as chronic appendicitis. This view is supported by Carnett in the *American Journal of Medical Science,* 1927, clxxiv. 579. He says: 'I have been unable to find a symptom complex which warrants a preoperative diagnosis of (clinical, not microscopic) chronic appendicitis and which will be relieved by appendectomy. I am firmly convinced: (1) that 'chronic appendicitis' as ordinarily encountered under the microscope does not give clinical symptoms; (2) that the clinical symptoms which heretofore have been ascribed to 'chronic appendicitis' are not caused by the appendix, and are not physically cured by appendectomy. Psychic or fallacious cures are very common.'

Membranes, bands, &c. Jackson (319, 320) had observed in several cases complaining of right iliac pain, constipation, mucous colitis, and neurasthenia, that although the appendix was normal there was an abnormality present in its vicinity in the shape of a membrane. This membrane consisted of a transparent vascularized veil passing from the right parietal wall to invest the caecum and ascending colon. In it ran bright blood-vessels parallel to the long axis of the colon, which was freely mobile, but had the appearance as if it were imprisoned in a bag of membrane much too small to hold it.

Payr (492) had noted that the last part of the transverse colon may be attached to the first part of the descending colon in the neighbourhood of the splenic flexure in a somewhat similar manner. In none of the cases, however, in which it was observed were any definite symptoms attributable to it, and therefore Payr's membrane has received little attention from clinicians. Not so with Jackson's membrane, which was at once associated with the production of the vague right iliac pain and general symptoms said to have been due to chronic appendicitis.

Binnie (64), Hofmeister (282), Gerster (221), Pilcher (498), and others who agreed that it was the cause of these vague abdominal symptoms thought it to be of inflammatory origin. Dobson and Jamieson (167) showed this could not be correct since the path of infection would be by way of the lymphatics, and these run inwards from the bowel to the meso-colic vessels, away from the situation of Jackson's membrane. Mayo (429) suggested it was of congenital origin, resulting from the caecum and lower end of the ileum burrowing behind the posterior parietal peritoneum during their descent from under the liver. According to Morley (467) it is in some cases the continuation of the great omentum. The now generally accepted view is that it is a development anomaly. When

the caecum is still below the liver, the omentum grows down over the front of the transverse colon and adheres to it.

If by chance the right edge of the great omentum fuses with the lateral peritoneum before the caecum descends, the latter organ in descending will stretch out the attachment in the form of the thin membrane described by Jackson.

The early acceptance of this view led to active criticism of Lane's theory, that thickening of the left or under layer of the mesentery, two inches from the ileo-caecal junction, was a new formation on the part of nature to hold up a caecum and terminal ileum weighed down by the excessive bulk of their contents which resulted from stasis. Certain supporters of Lane's general theory could not agree with him in his view that these bands, 'by crystallization of the lines of force' develop as supporting structures to suspend an overloaded gut. Many followed Chapple (121), who held that they were the result of a local peritonitis induced by the intestinal stasis. Later work disproved both these views by finding the bands and membranes in individuals free from all the symptoms hitherto attributed to them.

Eastman (181) and Flint (207) in America, also Gray and Anderson (245) in this country found the band producing Lane's kink to be present in at least 10 per cent. of all cases coming to laparatomy, and in none of which were characteristic symptoms found in association with it. Pringle (504) demonstrated its presence in 20 per cent. of infants and embryos. Finally Reid (511) showed that Lane's band is merely the persistence of the embryonic genito-mesenteric fold, which passes from the terminal ileum to be attached to the posterior abdominal wall along the line of the right spermatic or ovarian vessels. According to Todd (590), there are to be found in many subjects accessory peritoneal bands which cannot be regarded as pathological. Of these, the three most consistently found are the phrenico-colic, the hepatico-colic, and Toldt's ligament or membrane. Toldt's membrane consists of a dense white band situated on the outer side of the loop formed by the pelvic colon, and superimposed on its mesocolon through which it binds down this loop of colon to the iliac fossa.

If it is incised, the mesocolon is found to be in a normal condition beneath it. This membrane is of considerable interest, since Lane holds it to be the first formed in the course of events he had described. He has referred to it as producing 'the first and last kink'. Its extreme frequency in the embryo and young child, however, shows clearly that it is of congenital origin. A fourth band may be referred to in passing, the cysticolic, which is present in one subject out of every four, and which connects the tranverse colon and duodenum with the gall bladder. This cysticolic band is supposed to be due to the fusion of the right edge of the great omentum with the lateral peritoneum after the caecum has descended. Bryant (87–8), who made exhaustive search in cadavers, found developmental adhesions very common in all sorts of situations. He found them in no less than 91 per cent. of all bodies examined, and in as many as 65 different positions. These developmental adhesions he found remain constant up to about 40, but after that age the peritoneum seems to take on an

increased capacity for fusing, and a sudden increase of 50 per cent. then occurs. This possibility was suggested by Keith (343), when he pointed out that the cells which line the peritoneum have in themselves, as an inherent quality, the power to form adhesions at any period in the individual's lifetime similar to what they have done in the past during man's evolutionary history.

The acceptance of these membranes, bands, &c. as congenital structures at once raises the question, Do they or do they not cause obstruction? Anatomists, clinicians, and radiologists like Keith (340), Hurst (301), Barclay (40), Mixter (456), Schwarz (545), and Carman (110), and many others are unanimous in stating that they have never found them obstruct the onward passage of the intestinal contents in the slightest degree.

Mobile caecum. In 1904 Haussman (266) reported eight cases of right iliac pain with constipation, in which he could find no pathological changes in the appendix, but did find an abnormal mobility of the caecum and ascending colon. This undue mobility he assumed to be the cause of the symptoms. Albu (6) and Wilms (635–6) reported similar cases, and the latter devised an operation for fixing the caecum. On the continent 'caecum mobile' was readily accepted as a clinical entity, until Klose (353–4) reported that of twelve cases with identical symptoms, all supposed to be pathognomonic, of mobile caecum, three showed the caecum not mobile but fixed down by adhesions. Sailer (536) in 1912 reviewed all the literature which had appeared up to that time and found the evidence for the existence of this clinical entity 'not proven'. It will be remembered that before the fourth month of foetal life the midgut loop, i.e., the gut from the duodenum at the opening of the common bile duct to the splenic flexure, is suspended from the midline by a single dorsal mesentery, of which the superior mesenteric artery forms the axis. Some time between the fourth and the fifth month this loop undergoes a counter clockwise rotation round its axis. The caecum, originally a diverticulum on the posterior limb of the loop, swings round three-quarters of a circle until it comes to lie in the right hypochondrium, under the liver. Here it may remain undescended, or occupy any one of a series of positions from there down to the true pelvis. After attaining its final position, the ascending colon and hepatic flexure are generally bound directly to the parietes by a layer of peritoneum without the intervention of a mesocolon, which the caecum, on the other hand, almost invariably possesses.

G. M. Smith (564), who made a careful examination of 982 cadavers, found that in 17 there was no attempt at direct fixation of the ascending colon and that the whole of the proximal colon possesses a mesentery. In 304 others a mesentery was present with, however, some attempt at fixation near the hepatic flexure. In other words, a condition favouring caecum mobile is present in no less than one-third of all individuals. Nevertheless, surgeons like Waugh (617), Morley (468), and Carslaw (111) attribute the production of symptoms to such a state of affairs, holding that an organ which is not fixed is at a mechanical disadvantage compared with a fixed one. Flint (204–5) has pointed out it was early recognized in Leeds, that of two patients with identical symptoms, one

might have an unduly mobile colon, and the other an unduly fixed colon; also, what is still more important, that the fixation of the one, and the freeing of the other, equally failed to remove the symptoms of which the patient complained. This observation strongly negatives the view that a mobile caecum is in itself necessarily productive of symptoms. Carson (112) probably expresses the considered judgement of the majority of surgeons to-day, when he says that all the abdominal organs should be capable of some degree of movement, and that fixation of the kidney, colon, or stomach is contrary to nature. We shall see later that the physiological integrity of the colon is quite independent of its position and mobility.

Synthetic theories. Several observers who felt that Lane and Goldthwait theories explained too much, while other recent theories did not explain enough, attempted a synthesis of the viewpoints in each which appealed to them. Thus Coffey (135), in his monograph on gastro-enteroptosis, accepts the Goldthwait view that the viscera are retained by the abdominal wall holding them on the psoas shelf, but differs from him by holding that these factors are only of secondary importance compared with that of complete peritoneal fusion. Where the fusion is complete, ptosis cannot occur, no matter how the individual may carry himself. Accordingly, he divides all cases of visceroptosis into (*a*) general, where fusion is completely lacking, (*b*) right-sided, where the ascending colon alone has failed to fuse, and (*c*) midline, where the omental bursa has failed to become obliterated and produce a gastro-colic ligament to support the transverse colon. Contrary to the classical view, he regards the flexures as the last parts to drop, and it is because they remain fixed after the remainder has fallen that kinks are produced which lead to intestinal stasis.

On the other hand, where there is total lack of fusion, there may be no symptoms, since there are no fixed points over which the gut may kink. Symptoms, however, may appear in time because bands and membranes develop sooner or later in an attempt to hold up the falling viscera. Kinks may then develop around these. He supports Longyear (404) in recognizing the existence of a nephro-colic ligament, and agrees with him that nephroptosis is always secondary to coloptosis, the kidney being dragged out of place by its attachment through this ligament to the prolapsed colon.

Walton (611–12) in a series of papers puts forward the opinion that visceroptosis is a combination of several factors. He accepts the fact that membrane formation and increased mobility are not in themselves causative of the condition. Also an inherited mental and physical weakness is nothing more than an accessory factor, otherwise the condition would be as common in men as in women. Faulty development of the postural mechanism is for him the fundamental factor. The condition is commoner in women because young girls receive such poor training of their static muscles that a large number grow up with defective postural tone. Walton departs from the Goldthwait theory by recognizing that all individuals with this deceptive tonus do not experience symptoms. The production of these he explains as follows: When the viscera drop in these

individuals, no symptoms develop unless they are unfortunate enough to possess one or more of the already-described congenital bands. If they do, then when the viscera drop, the intestines become irregularly kinked and symptoms arise. He sees the difficulty that no hypertrophy of the muscular coat can be demonstrated proximal to the bands, such as would be expected if they were causing a mechanical obstruction. This he overcomes with the suggestion that the bands cause obstruction by inducing areas of localized spasm of the circular coat of the gut. In his most recent contribution he claims that this is brought about by overaction of the sympathetic system from local irritation by the band.

Cawadias (118), accepting the fact that large numbers of healthy individuals have low viscera, suggests that the term visceroptosis should be applied only to the condition when the dropped viscera originally occupied a high position. This seems a distinction without a difference, since few, if any, individuals, possess a record of the position of the viscera before the onset of their symptoms. Although symptoms as a rule do not appear before puberty, these synthetic views initiated efforts to recognize the condition in early life and link up the vague digestive symptoms of childhood with those of the adult.

Koenig and Mankell (356) suggested that many of the cases of chronic intestinal disorders in children of 3 months to 15 years of age were due to visceroptosis. Kerly (348–9) reported sixty cases with X-ray findings.

Talbot and Brown (585), in a similar series of cases, gave a Goldthwait interpretation to them and claimed that by training in posture and carriage, not only were the symptoms removed, but the viscera were restored to their normal position.

De Witt Sherman (555) independently came to the same conclusion, and Mosher (470) claimed that in all children with chronic digestive symptoms the ratio of sternum length to the length of the sterno-pubic line was that characteristic of the enteroptotic habitus. Quite recently Le Wald (398), investigating forty-four cases of cyclic vomiting, reported finding a dilated ptosed stomach in twenty-three and an elongated ptosed colon in thirty-five. He suggested that cyclic vomiting should be regarded not as a manifestation of disordered metabolism, but as a system of visceroptosis. These views failed to take account of the normal radiologic differences between the child and the adult.

Rogatz (521) confirmed the previous findings of Leven and Barret (396), Flesch and Peteri (203), Trumpp (595), Simmonds (558), and others that in infancy the stomach lies in a horizontal plane until the child stands and walks. After then it assumes the vertical form in 75 per cent., but may display a wide variety of shapes and positions within the range of normality. He showed that a stomach of apparently poor muscular tone and contractility could be converted into one of different shape, tone and motility, by altering the diet.

According to De Buys and Henrique (98) and R. R. Smith (565) the stomach does not assume permanently the adult shape until 3 years of age. Wright (641) examined 250 normal children of 6–15 years of age, and noted that

as the child gets older the stomach tends more and more to assume the J-shape, characteristic of adults. In 42 per cent. the greater curvature was above the iliac crests, in 42 per cent. below, and in 16 per cent. at the level of the crest. In none was there any relationship between the child's body build and the position of the stomach. He noted that a palpable liver and right kidney was a common finding at all ages. After 11 years of age the stomach in girls tended to lie at a lower level than in boys. He failed to observe any relationship between the position and shape of the stomach or other viscera, and the production of digestive symptoms.

None of the theories so far considered have successfully withstood the test of time, chiefly for the reason that they were based upon anatomical and mechanical conceptions of disease which left out of account physiological reactions. Clinical research is daily stressing more and more the fact that there is no necessary parallelism between change in structure and change in function, and that the essence of disease is essentially a disorder of function.

This is well expressed in the words of Sir Thomas Horder (287). 'We are passing through the stage of incrimination on the score of disease, to that of tolerance on the score of variability in individuals, and we may yet arrive at the stage of indifference, on the score of a changed conception of the standard of health. There are variations, of great physiological significance, in the same individual at different times, and under different conditions.'

The adverse criticism directed towards these theories and the alternative views proposed, require a brief review before considering the more recent purely physiological conceptions.

A Criticism of the Mechanical Theories of Visceroptosis.

We have seen that long before Lane the idea had originated that intestinal angulations produce delay in the progress of food material through the alimentary tract, and that a stasis results which leads to the absorption of poisons formed within the intestine. However, the lengths to which he developed his ideas, and the sweeping nature of his conclusions, stimulated intensive investigation of their fundamental assumptions. This critical investigation revealed many untenable positions, and laid the foundation of a physiological interpretation of visceroptosis on a functional basis.

Lane (379) defined stasis as 'such a delay of the contents of the intestines in some portions of the gastro-intestinal tract, but more particularly in the large bowel, as allows the absorption into the circulation of a larger quantity of toxic material than can be dealt with effectually. This delay results from a mechanical alteration in the normal arrangement of the drainage apparatus.'

Einhorn (185) in America, where Lane's views were early accepted, produced evidence to controvert the assumption that the digestive canal is merely a drainage tube, and was supported by Bassler (65), who reported 167 cases of Lane's kinks, in only five of which was constipation or symptoms of stasis present.

However, Jordan (325), who enthusiastically supported Lane, claimed that the following radiological signs were absolutely diagnostic of intestinal stasis, irrespective of the presence or absence of symptoms.

(1) Dilatation and writhing peristalsis of the duodenum.

(2) Ileal stasis with delay of the intestinal contents in the terminal ileal coils.

(3) Kinks evidenced by localized narrowing, fixation, tenderness, and dilatation proximal to the stenosis, and delay in the passage of the intestinal contents.

(4) New-formed bands about the appendix, kinking and fixing it.

(5) Elongation, dilatation, and looping of the pelvic colon.

Without waiting for a decisive answer to the question whether these radiological appearances were normal or abnormal, surgeons seized upon the idea of ileal stasis as a pathological phenomenon, since apparent delay at the lower end of the ileum was frequently such a striking feature on screening the abdomen. We have seen in the previous section that Lane's views of band formation were not readily accepted by the majority of surgeons, who sought for some other explanation of this ileal delay. Thus adhesions following acute appendicitis or the presence of chronic appendicitis were regarded as the cause by Hurst (294–5), George and Gerbert (219–20), while Case (114–16) and Kellog (344–5) suggested an incompetence of the ileocaecal valve, and Cole (137) supposed it to follow upon constipation in the proximal colon.

This idea of ileal stasis and ileal regurgitation was no new thing in medicine. Posthius (500) in 1566 described the valve, and Varole (599) in 1570 suggested that its function was to prevent the regurgitation of faeces into the small intestine. In 1586 Piccolomini (497) produced experimentally actual incompetence of the ileocaecal valve. Interest in the structure remained dormant until 1822, when Good (239) showed that the active muscular sphincteric function of the mechanism at the distal end of the ileum is to moderate the flow of the contents of the small intestine into the colon. In 1897 the incompetence of the valve was suggested as a clinical entity by Hertz (278), but it was not until 1914 that its existence was actually demonstrated in the living subject by Cole (138) and Case (114).

Hurst (296) was the first to show that chyme reaches the end of the ileum one hour or longer before any appreciable quantity passes into the caecum, and that the ileum is often still full four to five or more hours after the last traces of the opaque meal have left the stomach. During this period of ileal digestion active segmentation but no peristalsis is to be observed. He asserted that intestinal stasis does not lead to duodenal kinking, dilatation, or ulceration, and points to the fact, since well established, that duodenal ulcers are associated with an unusually rapid passage of chyme out of the stomach and through the whole of the small intestine, rather than with delay. He also says that when the stomach empties rapidly the duodenum contains more barium at a given moment than it usually would do. Hence it appears dilated, and the normal peristalsis and segmentation are rendered more clearly visible, this accounting for the so-called

'writhing'. Segmentation in the terminal ileum is very active, and this, Hurst thinks, may be mistaken for an organic narrowing. As to incompetency of the ileocaecal valve, he feels that the valve does not normally prevent regurgitation into the ileum, as he has seen this occur with a pressure as low as one foot of water.

Barclay (40), protesting against the conception of 'water-tight' compartments with anatomical boundaries in the alimentary canal, holds that food passes into the caecum by pressure from behind, and that the ileocaecal valve, not only prevents regurgitation, but regulates the flow into the caecum. That is to say, ileal stasis, up to a point, is physiological. He finds that the time in which food reaches and leaves the terminal ileum depends on the rate of emptying of the stomach. In duodenal irritation food may reach it in a few minutes, whereas in delayed emptying of the stomach an indefinite time may elapse. Moreover, an accumulation of faeces in the caecum will give rise to back pressure and produce a temporary ileal stasis which is immediately removed by an enema or purge. He also pointed out that the terminal 4 in. of the ileum gives a shadow quite different from the rest of the small intestine, probably because the circular fibres there are more evenly developed and their tonic action more persistent. He agreed with Hurst that the taking of food into the stomach tends to make the ileum empty into the caecum, and that conversely, where there is true obstruction from old inflammatory changes in the ileocaecal region, there is delayed emptying of the stomach. In no case examined did he find any evidence that Lane's kink increased the emptying-time of the stomach.

Notwithstanding these observations, Kellog (344), imbued with the idea that the essential factor in intestinal stasis was an insufficiency of the ileocaecal valve, devised operative procedures to render it competent. Case (117) with further experience revised his previous views on ileocaecal incompetence, and along with Baetzer (29–30) and others showed that the so-called incompetence to enemata was a normal phenomenon.

Jones (324), on the clinical side, undertook an exhaustive study of a series of cases in which the X-ray picture of ileocaecal regurgitation was a prominent feature. He found in his group of 315 females and 185 males that a strikingly high percentage of them were of asthenic build and showed undue colonic mobility. Only 70 per cent., however, complained of symptoms, but the relief of the regurgitation did not remove them. On the other hand, some of the most pronounced and persistent cases of regurgitation had no symptoms. Ranaudeux (512) in France conclusively demonstrated that ileal stasis is best regarded as a transient or recurrent phenomenon, depending on the state of irritability of the colon more than on any other single factor. He holds that it is of physiological, rather than pathological, significance. He also showed that in cases of out-and-out mechanical obstruction in the ileocaecal region, ileal stasis may be conspicuous by its absence.

Kantor (331) has recently revised the whole concept of ileal stasis. He points out that the determination of the normal ileal emptying time is difficult since

it represents the sum of two variables, namely the emptying of the stomach plus the emptying time of the entire small intestine. He finds that incompetence of the ileocaecal valve to enemata is no indication of stasis since it occurs in the same percentage in individuals without symptoms, as it does in those with symptoms, that is, approximately 44 per cent. of all persons examined. Taking four hours as an arbitrary normal emptying time, Kantor found delay in 100 out of 161 so-called 'stasis' cases. This series comprised an equal number of males and females with an age incidence of thirty-one to forty years. He found no relationship to habitus, but did find, contrary to all previous observers, that ileal stasis was much commoner in individuals with a high caecum and short, fixed colon, than in those with a low caecum and mobile colon. In 63 per cent. of his cases the appendix has been removed. Constipation was only complained of in 45 per cent. of individuals showing ileal stasis, whereas it occurs in nearly 60 per cent. of all cases with dyspeptic symptoms. In every case the filling of the colon was well advanced by the sixth to ninth hour, and no signs of kinks or adhesions could be detected. In a later paper he confirms Renaudeux's view that it is a recurrent transient phenomenon, and finds that the commonest cause of it persisting is an unrecognized colitis. He holds that some colons are so weak constitutionally that even an ordinary mixed diet irritates them. This irritation is sufficient to cause a functional disturbance which manifests itself by so-called stasis symptoms.

Carman (110) reported that between 1913 and 1917 hundreds of cases of intestinal stasis were examined at the Mayo Clinic, and that no obstructive kinks were found on radiological examination, nor were any discovered by the surgeon in those cases which were explored. Angulations of the bowel were noted repeatedly, and in certain planes of view these sometimes seemed to be acute and potentially obstructive, but when observed from another direction the course of the bowel was seen to be curved instead of angular, and no stenosis existed.

Rowden, who examined all the cases X-rayed at the Leeds General Infirmary between 1911 and 1922, in a verbal communication informs me that he agrees with Carman, and that he has never seen the duodenal writhing of Jordan.

On the question of duodenal stasis Wingate Todd (591) recently wrote as follows: 'While it is not the intention of the writer to deny duodenal stasis with its serious consequences, we do want to point out most emphatically that pseudostasis is not uncommon in the normal healthy subject. We have met with it in students who are in perfect condition. Sometimes it is quite temporary, lasting only a short while, sometimes it is present throughout the hour. Many students can produce temporary stasis by voluntarily contracting the abdominal wall and raising the viscera. When the effort is relaxed the stasis ceases. When a stasis of longer duration occurs it is due to a temporary constriction of the duodenum, not by the weight of the small intestine pulling on the mesentery, but by gas, usually in the transverse colon, causing an indirect pressure on the duodenum. This itself is one result of subconscious nervousness.' True duodenal stasis, when it does occur, is, according to Bloom and Arens (68), a radiologic

sign seen in various definite pathological conditions, of which the commonest are cholecystitis, gall stones, and duodenal ulcer.

Finally, there is the question of the elongated, dilated, looped pelvic colon. Treves (592) long ago pointed out that anomalies in the length of the colon are a common finding in healthy individuals. Bryant (89) found that the human intestine may vary in length to an extent of 100 per cent. from the average and confirms Vietor's (603) observation that these variations are present before the fifth month of foetal life. He finds that after birth the colon continues to grow throughout life. Miloslavisch (455) has shown that the more extreme variations in the length of the intestine is a racial characteristic. Larimore (390) agrees with Bryant that when the length of the colon exceeds the body-length of the individual it must throw itself into loops to accommodate itself to the abdomen. He examined 502 healthy adults and found the following percentage of variations; redundancy of the ascending colon in 0·02 per cent., and of the hepatic flexure in 2·8 per cent.; an absence of the hepatic flexure in 2·1 per cent.; redundancy of the transverse colon in 3 per cent. of the splenic flexure in 3 per cent., of the descending colon in 1·4 per cent., and of the sigmoid in 18 per cent. He found no relationship to body habitus, but did find that in individuals with a distal redundancy motor delay was twice as common as in redundancy elsewhere and twice again as common in females as in males. On the other hand, in patients with symptoms Kantor (330) found redundant colon present in only 62 out of 1229 cases and believes that two-thirds of all individuals who possess redundancy never have any symptoms associated with it. He also finds that of the patients with symptoms the majority are males or females of sthenic habitus. Both Kantor and Larimore consider that the so-called low caecum is simply an elongated ascending colon and not a ptosed caecum, since it is only found in 37 per cent. of individuals with low stomachs and low transverse colons.

Bryant had pointed out that the physiological constipation of advancing years appears to be associated with the length of the colon increasing with age, and in this view was confirmed by Larimore and Kantor. Harvey (265) and Davis (159) were of the opinion that three-quarters of the cases of elongated caeco-colons had no mesentery, but Kantor found that a mesentery was present in half of his cases.

While these observations were gradually demolishing the time-honoured conceptions of a mechanical obstruction delaying the faecal passage the combined attack of the physiologist and the radiologist on normal gastro-intestinal function were eliciting many new facts which served as a starting-point for the newer, or physiological theories of visceroptosis, and intestinal stasis.

Physiological Theories of Viceroptosis.

Before dealing with these in detail it is desirable to review briefly our present knowledge of the motor functions of the gastro-intestinal tract.

Starting with the stomach, the earlier workers held that a typical gastric movement consisted of two distinct phases, (*a*) a peristaltic wave which in-

volved the body of the stomach and preantral region, partitioning the stomach at the incisura angularis; (*b*) a contraction of the musculature of the pyloric antrum as a whole. Cannon (107) then attempted to show that this was not correct. What actually happens is that a single peristaltic wave sweeps from its origin on the body of the stomach to the pylorus without partitioning the stomach.

McCrea, McSwiney, Morrison, and Stopford (437) find that both schools are correct, and that not only are the two types of movement to be seen in man, but occasionally a third variety, in which shallow waves pass on over the formed antrum after the formation of the constriction at the incisura. However, in rabbit and man the two-phase movement is the common one. This observation led these workers to conclude that functionally the stomach consists of a proximal, quiescent reservoir which shows only slow alterations in volume, and a distal, active motor region. The reservoir is composed of the fundus and the proximal portion of the body, i. e. the cardiac region of the stomach.

The distal motor segment consists of the major portion of the body with the pars pylorica. There is no anatomical division between these two parts, but a well-marked functional one is produced by the formation of the incisura angularis.

The observation that a stomach with true achylia empties as fast, if not faster, than one with average hydrochloric acid contents caused McClure, Reynolds, and Schwartz (435) to abandon the classical view of the acid control of the pylorus. Alvarez (13–15) showed that it is probable that the opening and closing of the pylorus depends to a large measure on mechanical factors, i. e. differences in the gradient of tone and irritability between the stomach and duodenum. Wheelon and Thomas (625) confirmed this, and found that like the rest of the intestine, the acts of opening and closing of the pyloric sphincter are to a great extent dependent upon the motility of structures lying on either side. This means that the sphincter acts as a functional link in the chain of forward conduction of material from the stomach. The antrum, pyloric sphincter, and first part of the duodenum each possesses definite rhythmic cycles which bear a constant relationship and show a dependence on one another so that parts excited craniad travel caudad to excite the lower segments. These three portions, therefore, show progressive motility which occurs in a definite sequence, and which in man normally causes material to leave the stomach and be delivered into portions of the intestine below the first part of the duodenum. Towards the end of digestion the tone of the stomach probably falls below that of the rest of the tract and permits the normal regurgitation of the duodenal contents into the stomach.

When we pass to the small intestine we find that the apparently well-established 'law of the intestine' of Bayliss and Starling has not escaped adverse criticism, notably by Alvarez. The law states that—'If cerebral reflexes be excluded, excitation at any point of the gut excites contraction above, inhibition below'. Alvarez (15, 17) observes that the few men who have

written on the subject all report that the demonstration of this reflex is not easy, and that it is often absent, atypical, or reversed. Instead of the classical three forms of movement occurring in the small intestine (*a*) segmentation, (*b*) slowly advancing contractions preceded by inhibition, (*c*) peristaltic rushes, Alvarez brings evidence to show that there are only two (*a*) segmentation, and (*b*) peristaltic rush.

The investigations of Alvarez show that the rhythmic intestinal contractions are not of uniform rate, but vary inversely with the distance from the pylorus. For example, the contractions of a segment of the duodenum proceed at a more rapid rate (17–21 per min.) than do the contractions of an ileal segment (10–12 per min.) under the same experimental conditions. Associated with the variations in frequency are also differences in the amplitude of the contractions of the intestinal muscle. As the contractions become less frequent, their amplitude increases to the extent that the ratio between the amplitude of the contractions of duodenal and ileal segments is as 3 to 20. Tone and irritability diminish progressively from duodenum to ileum. He finds a direct relationship between the frequency of rhythm and the metabolism rate of intestinal muscle, and shows that this direct relationship is in favour of the view that the intestinal contractions are myogenic in origin and not neurogenic. The graded activity of the muscle with regard to rhythm, tonus, and irritability is probably an important factor in the production of peristalsis, and in determining the direction which this movement shall take. The resistance which is usually found springing up ahead of the advancing wave serves the purpose of keeping the bowel from emptying too rapidly.

The striking feature of the colon is the entire absence of movement it presents in contrast to the active small intestine. Only at long intervals may waves occasionally be seen, and most observers are now in agreement that true antiperistaltic waves never have been observed in man.

Barclay (39, 40), Mills (453), Alvarez (15), Hurst (305), &c., are of opinion the caeco-colon fills from the pressure of material entering from the ileum. Mills and Soper (454) claim to have noted a certain amount of 'puddling' taking place in the caecum.

The consensus of opinion is that the more solid part of the faecal column occupies the centre of the lumen and is surrounded by the more fluid part. Welch and Plant (620) investigating the activity of the colon by means of balloons find that it consists of irregularly recurring changes in tonus, usually with super-imposed contractions.

These presumably serve to bring the fluid peripheral part of the column into more intimate contact with the mucosa through the formation of haustra. When the bowel was normally full the taking of food by mouth always increased these muscular movements, but when it was empty no change could be detected. Placing of food in the stomach through a fistula had no effect, showing that this movement is of psychical origin and is not a physiologic reflex from distension of the stomach by food.

This responsiveness of the colon to psychical effects was also noted by Gilbert Scott (548), who found by opaque enemata that its tone varies according to the mental attitude of the patient. The fear of not being able to retain the enema may produce such an increase in tone as to amount to spasticity. When the individual is reassured, the apparently hypertonic colon may become atonic. The contents of the colon are said to be moved onwards by mass peristalsis and not by the above-mentioned activities. The mechanism of this movement, observed independently by Holzknecht (286), Barclay (39), and Hurst (294) appears to be (1) relaxation of the tonic action of the muscular coats with disappearance of haustration, (2) a big peristaltic wave, which sweeps the whole contents along into the pelvic colon. This movement takes place once or twice a day, without subjective sensations of any kind, and without producing a call to stool. The wave appears to begin at the hepatic end of the transverse colon and end at the pelvic colon.

However, Wingate Todd (591), by taking successive radiograms of the proximal colon at intervals of two minutes and submitting these to cinematographic treatment was able to observe a slow peristaltic wave. This wave passes over both caecum and ascending colon during filling, with alternate definition and obscuration of the haustra. He never saw antiperistalsis. The same peristaltic wave was seen in the transverse colon. The slow progress of peristalsis modifies but does not obliterate the haustra. The wave progresses at about half the speed of peristalsis in the stomach. He never saw the mass movement described by Barclay, &c., and concludes that the contents are moved along the proximal colon by slow peristalsis in a precisely similar fashion to the movement already recognized in the stomach and small intestine.

Mayo (430), Soper (567), and others have shown that the recto-sigmoid portion of the gut has a definite mechanism which retards the faecal current from entering the rectum. As we have seen above, the taking of food increases the tone of the colon if it is full. This increase in tone above a certain point produces a relaxation of the recto-sigmoid sphincter which allows the faeces to enter the rectum and produce the call to stool.

The present state of opinion regarding the innervation of the gastro-intestinal tract and its action on the sphincter is somewhat as follows:

The classical view is that the cardiac portion of the stomach is supplied by the parasympathetic system which carries both motor and inhibitory fibres. In the pyloric region the sympathetic supply first becomes evident, and from this point onwards, as far as the ileo-caecal region, there is a combined distribution of sympathetic and parasympathetic elements, the former motor, the latter inhibitory in effect. The large intestine, as far as the lower end of the pelvic colon, is said to be the site of a pure sympathetic supply, motor and inhibitory impulses being carried by the sympathetic fibres. The remaining portion of the large intestine and the rectum combine a sympathetic and a parasympathetic supply, the former being inhibitory and the latter motor.

These two systems are supposed to be antagonistic and balanced in action.

Any disturbance in this balance upsets the function of the gastro-intestinal tract and produces symptoms. Many investigators have looked to a disturbance of this autonomic balance as the real cause of symptom production in visceroptosis. Thus, in 1910, Eppinger and Hess (189) picked out from cases of neurasthenia and hysteria with digestive symptoms, a clinical syndrome which they termed vagatonia characterized by constipation, asthenic dyspepsia, hypersection, and pyloric spasm in pale-faced nervous individuals. They held that normally a balance exists between the action of the parasympathetic and the sympathetic nervous systems, and that this balance may be disturbed by the one or the other system predominating. Believing that the sympathetic system was normally activated by adrenalin, they assumed the existence of a hypothetical endocrine substance, called autonomine, which, when present in excess in the body, produced the symptoms by over stimulation of the parasympathetic. They based their diagnosis on the supposed sharply selective action of certain drugs on the autonomic nervous system. Lewandowsky (399) as early as 1913 disproved this selective action, and was confirmed by Barath (36–7), who demonstrated in the case of calcium and adrenalin an amphotropic action.

It is now known that the action of adrenalin is not essential for the functioning of the sympathetic. Hoskins (288), summing up the evidence for and against, finds that adrenalin at most merely reinforces the effect of normal sympathetic impulses, and that the sympathetic system can do of itself everything that can be accomplished by adrenalin. In a more recent contribution he states that the most plausible assumption is that adrenalin consistently and generally exerts a biphasic effect, serving, if present at all, as a sympathetic sedative. Under other conditions its stimulating effect would come into play.

Sharpey-Schaefer (548), in his review of the dual control of tissues, states that the neural control is the primary one. The humoral control is in many cases a useful, and even a necessary, auxiliary in maintaining an effect initiated by the neural, and thus economizing the expenditure of nervous energy. Pachon (489) and Laignel Lavastine (368) find that numerous experimental facts are contrary to the conception of a neuro-glandular system in which the autonomic nervous system and the endocrine glands are intimately related, and in which the former is controlled by the latter. The action of the autonomic nervous system on internal secretion is simply a part of nervous regulation in general. However, there is a certain amount of evidence that nervous impulses may liberate chemical substances which stimulate the intestinal musculature. Thus Magnus (414) states that Le Heux working in his laboratory found that stimulation of the vagus liberates cholin in the intestinal wall, and this may act as a regulator or intestinal pacemaker. Be that as it may, the Eppinger and Hess theory in its entirety has never received serious consideration. On the other hand, many have sought to explain the production of symptoms by over action of one or other of the systems induced by stimuli other than chemical. Tyrrel Gray (247–8) sought to combine a mechanical theory with a functional theory based upon over action of the sympathetic. In his earlier paper he held that

the various degrees of prolapse represent variations in a gradual transition from the type found in quadrupeds; the final position in man being one of accommodation to the erect posture, altered food requirements, and so forth. Therefore, ptosis and undue mobility are not pathological, but only predispose to symptom production. Symptoms are absent until either the abdominal wall or pelvic floor give way and allow the viscera to drag upon the mesentery. This mesenteric drag produces intestinal inhibition through the autonomic nervous system, resulting in intestinal stasis and overloading of the bowel. This overloading of the bowel increases the drag upon the mesentery and thus a vicious circle is set up.

In a later contribution he assumes that in a pure neurosis the effect of the emotion is to cause excessive adrenalin secretion leading to exhaustion of the adrenals. This results in suppression of the pancreatic function, which leads to a diminution of the efferent vagus impulses from this gland. In consequence, there will be a diminution in the efferent impulses going to the bowel, leading to defective secretion and peristalsis with consequent stasis. In passing it may be stated he offers no experimental evidence in support of this theory, which, in consequence, is distinctly unconvincing. When there is no visceroptosis, kinks, or bands present, psychotherapy may relieve this condition of affairs. But not so in the presence of bands and membranes, since the loaded bowel will pull on them and initiate a direct local or a general reflex sympathetic inhibition, so that a secondary vicious circle is established. Tyrrel Gray appears, therefore, to have abandoned the view that the drag on the mesentery is productive of symptoms. Such a view is untenable, considering the fact that in an individual whose abdomen is open under local anaesthesia the slightest drag on the mesentery will cause agonizing pain quite different from the ache complained of by the visceroptotic. Again, if a cadaver, which in life had apparently a total absence of muscular support by the abdominal wall and pelvic floor, be opened in the erect posture, the viscera have to drop a considerable distance beyond the boundaries of the intact abdomen before a strain on the mesentery can be detected. Finally, since loops of intestines ligatured and placed in water float, it is impossible to see how they can drag on the mesentery in the intact abdomen where, in addition, exists a negative intra-abdominal pressure. Fraser (210) considers that while the exercise of the antagonistic functions between the parasympathetic and sympathetic systems is general, it is exercised especially in those regions where a special arrangement of the muscle fibres exist, namely at the sphincters. He regards the parasympathetic as the older system, since it subserves localized function, while the sympathetic is later developed to subserve a diffuse and widespread reaction. The sympathetic or inhibitory system is not completely developed at birth, hence there may then develop over action of the parasympathetic system. This lack of balance may appear at any time of life and be responsible for the functional disorders of the gastro-intestinal tract. Langdon Brown (81) is content to say that the motor disturbances of the alimentary tract may be expressed under the heads of irregular and exaggerated

contraction, tonic spasm, and atony. He holds that irregular and exaggerated contractions are due to the irritation of the parasympathetic system; when this occurs in the vagal area colic results, and when in the pelvic area tenesmus. Tonic spasm and atony are both due to sympathetic irritation. This irritation expresses itself by excess of normal movements at the sphincters, producing spasm, and by deficiency elsewhere, producing atony.

A quite recent contribution to this subject comes from T. Stacey Wilson (638) in his book on *Tonic Hardening of the Colon*. According to him, in certain states of the nervous system micro-organismal activity in the colon induces a state of 'elastic fixation' of the colon muscles. When this occurs abnormal stimuli radiate from the hardened colon. These, acting through the autonomic system, may produce the most profound disturbances in gastro-intestinal function. On the other hand, they may pass direct to the central nervous system and through it cause symptoms in other parts of the body as well as in the psychical sphere. This is 'proved' by always finding the pelvic colon contracted in such cases, and by the disappearance of symptoms when the colon relaxes. In view of the fact that the colon may be found contracted at one time and relaxed at another in the same individual, irrespective of the presence or absence of symptoms, it is not likely that 'elastic fixation' plays an important part in symptom formations.

The very term autonomic suggests an isolation of this nervous system as a self-contained unit, independent of the central nervous system, which functions as an 'abdominal brain'. Hence it is easy to push our ignorance one step further back and assume a lesion or disorder of this isolated, self-contained, nervous system as the explanation of functional symptoms in the area of its supply. Macleod (410) reminds us, however, that, because the neurons of the autonomic system are organized somewhat differently than are the efferent paths to skeletal muscle and innervate organs of different functions, the mistake should not be made in thinking that it acts independently of the central nervous system. Langley (387–8) conclusively proved that there are no commissural fibres between the different sets of sympathetic ganglia, such as would have to be present if these ganglia were to mediate like an 'abdominal brain'. Abel's work (1) also supports this view on the embryological side.

The functions of the connector fibres in the autonomic system would appear to consist largely in adjusting the activity of these structures, as a whole, to the conditions of activity brought about in the somatic musculature. Correlation takes place between visceral activity and somatic activity, so that the closest co-operation can be obtained between the organs of the body. There are times when the animal needs as a whole to communicate with its gastro-intestinal tract or one end of the tract with the other, and for this purpose the autonomic nervous system is utilized. Cohn (136) suggested the vagi carry feelings of hunger to the brain; Loeb (107) that they carry the impressions which make the animal feel comfortable and sleepy, and Cannon (107) that they help in adjusting the tone of the stomach to the food entering it, and carry the stimuli

which give rise to the psychic secretion, If the food is to be rejected they carry the impulses which bring the abdominal muscles into action. He also thinks the splanchnics serve to quieten the tract and stop digestion when the body is distressed or injured. McDowall (438) says it is clear that a balance between the parasympathetic and sympathetic is not essential to life, since the stomach can empty itself when all extrinsic nerves have been severed. McSwiney (438) looks upon the vagus as regulative rather than essentially motor. Alvarez (15) reminds us that the stimulation of the vagus is not uniform in its effects; most often, after a short period of inhibition, there follows a long phase of unusual activity or movement. Carlson and Litt (109) confirmed previous observers in finding motor and inhibitory fibres enter the pylorus by way both of the vagi and splanchnic nerves. Their experiments show that states of spasm or atonicity of the pylorus may be caused by excessive activity of either vagus or splanchnic efferents, motor and inhibitory. They find that appropriate stimuli of all visceral sensory nerves induce a temporary spasm of the pylorus, even when the vagus is severed. They advance the view that the action of the visceral efferents (both sympathetic and parasympathetic), at least on some of the motor mechanisms, are association or reflex responses, and not simple peripheral responses like that of the skeletal muscle, or stimulation of the pyramidal tract. That is, the visceral efferents are in reality afferents to a local but diffuse reflex mechanism in the viscera. The prevailing view of a simple antagonistic action of the vagus and sympathetic system is not tenable for the stomach and pylorus at least. Motor or inhibitory effects on these regions of the intestine are produced by both the vagi and splanchnic systems, the character of the peripheral responses depending on the initial physiological state of the peripheral motor mechanism, analogous to the so-called 'postural reflexes' of the spinal skeletal system.

In this connexion it may be recalled Grey (249) showed that when the stomach of a living animal is distended by fluid the intragastric pressure shows very little change, even up to the point of rupture of the viscus, and that this seemed to be controlled, not by the extrinsic nerves, but by the nervous elements residing in the gastric wall itself. This may be the mechanism which determines the character of the peripheral response described by Carlson and Litt.

Grasset (243) ten years ago pointed out that physiologists had completely abandoned the ancient dichotomy of the nervous system into a cerebro-spinal part (with the brain as the essential organ) for voluntary conscious acts, and an autonomic (with its ganglia) for involuntary, unconscious phenomena. The motor effect of excitation of the cerebral cortex, he adds, does not limit itself to the contraction of the trunk muscles but reacts on those of the intestines, circulation, and glandular reservoirs. Ott (105) obtained an inhibitory action on the stomach by stimulation of the optic thalami and cerebral peduncles. Budge and Valentin (105) found intestinal movements amplified by stimulation of the corpora quadrigemina, and Bochfontaine (105) obtained movements of the intestines in dogs by stimulation of certain parts of the motor cerebral cortex.

On the peripheral side, King (350) has demonstrated that impulses from

the urinary tract, rectum, peritoneum, and certain skin areas, reflexly diminish the tonus and movements of the small intestine.

Barber and Stewart (38) had previously shown that stimulation of appendix, gall bladder, and duodenum reacts on the motor activity of the stomach. Delay in the development of the inhibitory apparatus as a whole during the early months of life when rigidity and spasticity predominate until myelization of the pyramidal tract is complete, is a normal phenomenon. It may be remembered that years ago Verworn, in his *General Physiology*, suggested that inhibition in general might be due to subminimal stimulation. The necessary training for its development would appear to be adequate stimulation centrally and peripherally. Where this does not occur, or for any reason is impossible, the development of inhibition lags. The success of thick cereal feeding in the pyloric spasm of infants is very suggestive that there may be some truth in this theory.

The conclusion to be drawn from the evidence here offered is, that the gastro-intestinal tract, functioning by means of its own inherent mechanism, communicates with the central nervous system through the autonomic nervous system. The double innervation by parasympathetic and sympathetic is, according to Arnau (27), Alvarez (15), and others, a development for the better regulation of the gastro-intestinal tract as a whole. The central nervous system makes use of the vagus to produce localized effects, and of the sympathetic to produce widely diffused ones. The network-like arrangement of the long non-medullated fibres of the latter allow a ready diffusion of impulses travelling either way.

In the earlier days of colectomy for intestinal stasis Keith (340) had the opportunity of examining a series of colons removed by Lane. He was struck by the absence of any pathological finding that suggested obstruction in the sense of the term used by Lane and his school. Remembering also that Murphy and Cannon had demonstrated that experimentally-produced acute flexures of the bowel do not cause delay in the passage of the intestinal contents, he sought another explanation of intestinal stasis. Keith (341–2) had found in the ileocaecal junction of the rat certain peculiar branching cells, intermediate between a nerve-cell and a muscle element. He had previously observed that true ganglionic cells are immigrant neuroblasts from the neural canal, and that they do not reach the myenteric plexus before the fourth month of intra-uterine life. From this he concluded that a myenteric plexus was a composite structure composed of ganglion cells, muscle cells, and a network of intermediate cells, and that it functioned in virtue of these intermediate cells as a pacemaker, as well as a conducting agent. He found plexuses well developed in the pyloric region of the stomach, on the lesser curvature, in the second part of the duodenum, in the distal part of the transverse colon, in the descending and iliac colon, and highly developed in the rectum. This led him to assume that food in passing along the alimentary tract was propelled through a series of zones or segments, each furnished with its own pacemaker and its own rate

of rhythmical contraction. When irregularities or blocks do occur we should expect to find them at the points where one rhythmic zone passes into another. It was precisely at such points where the Lane school claimed to demonstrate the existence of obstructive bands and kinks. To obtain an orderly propulsion of food these rhythmic zones must be closely co-ordinated in their action. Disturbance in any one segment upsets the rhythm in all the other segments. In other words, each plexus guards its segment in the same way as a signal box protects its particular section on the railway. If there is a delay anywhere, the segment above refuses to pass on its contents until the line is 'all clear' below.

Alvarez (11, 15) disagrees with Keith. He points out that Magnus (413), Gunn, Underhill (259), and others have shown that plexus-free intestinal muscle contracts rhythmically, and that digestion proceeds quite satisfactorily after section of the vagi and sympathetics, as soon as the shock of section has passed off. In view of this, and his own work already referred to, he concludes that the myenteric plexus is a fairly simple nerve network without synapses, centres, or reflex arcs, whose principal function is to expedite conduction. He can find no evidence in support of Keith's zones, nor of rhythmic domination of one segment by another. He concludes that gastro-intestinal symptoms are motor symptoms produced by either (*a*) speeding up, (*b*) slowing down, (*c*) complete stoppage, or (*d*) reversal of the gradient of tone, irritability, and rhythmicity, which he has demonstrated in the gastro-intestinal tract. Toxins, psychic influences, &c., may upset the gradient, increasing, lessening, abolishing, or reversing it. Thus the vomiting of enemata, an old clinical observation, can only be explained by complete reversal of the gradient. Kast (335) had demonstrated its presence by giving lycopodium in capsules at night and recovering the spores from the back of the tongue next morning. Rectal constipation, by raising the tone in that segment of the gut, causes a reversed peristalsis; the nausea, biliousness, and furred, coated tongue, result from the passage upwards of colonic contents. Heartburn results from reversed peristalsis carrying normal gastric juice up to the sensitive lower pharynx; globus hystericus from a wave of swallowed air meeting a regurgitant wave. The relief which follows belching occurs when these waves of reversed peristalsis are permitted to run themselves out. He assumes that psychical influences can depress the gradient in one area, and raise it in another. The disturbance in the smoothness of working which results is quite capable of explaining the pains, flatulence, &c., complained of by these patients.

Prior to the introduction of the fractional method of investigating the secretory function of the stomach, many patients in the group here considered were assumed to owe their symptoms to some disturbance in secretion. The classical researches of Pavlov, Starling, and Cannon, elucidated the mechanism of the production of gastric juice. Ivy (315) has shown it depends on three factors:

(1) Cephalic stimuli consisting of:

(*a*) Reflexes through the cerebral cortex (psychical).

(*b*) Reflexes through the thalamus, mid-brain, and medulla, caused by sight, smell, taste, chewing, and swallowing.

(2) Gastric stimuli from:

(*a*) Mechanical distension of the stomach even after section of the vagus and sympathetics.

(*b*) Chemical action on the gastric mucosa (by meat and meat juice).

(3) Intestinal stimuli.

A transplanted stomach was found to recommence secreting gastric juice two to six hours after a meal, suggesting that some substance in the food, or one formed *de novo* in the intestine after absorption, is responsible for the final phase of secretion. Prior to the discovery of what constitutes a normal secretory curve, much stress was laid upon hyperchlorhydria and anhychlorhydria as pathological entities existing in the absence of organic disease. Yet Ewald (193) had shown many years ago that patients cured of their symptoms of hyperchlorhydria showed the same high acid titre after treatment as before. Later, Hurst (293) conclusively demonstrated that the intact stomach is insensitive to the highest concentration of HCl ever found in the stomach, and that it is only when the gastric secretion regurgitates to reach the sensitive lower pharynx that the patient complains of 'acidity' and 'burning'.

Rehfuss (588–9) and subsequent workers have shown that just as there are marked variations in the position and contour of the stomach in health, so are there also similar variations in the motor and secretory function. Thus there is a normal 'slow' stomach and a normal 'fast' stomach: a normal hypersecretory, isosecretory, and hyposecretory type. Bennett (60) confirmed this, finding that normal stomachs give widely varying curves both from the point of view of emptying time and height of secretion.

Bell (58) sums up the general consensus of opinion by saying there is no longer any justification for the employment of hyperchlorhydria or achlorhydria in a diagnostic sense. Bloomfield (69), using a particularly delicate method and testing at 10-minute intervals, finds the acidity and volume of secretion remarkably constant for each individual, but that motility was extremely variable and did not show any constant features either as regards emptying time or gastric volume curve. He also found great variations in the gastric tonus on successive examinations. Moreover, a deficient ability to secrete acid was a frequent occurrence in a miscellaneous group of persons, and no clinical significance could be attached to it.

Bassler (47) examined the secretory curve of 172 cases of visceroptosis and classified it as normal in 51, as showing hyperchlorhydria in 47, hypochlorhydria in 68, and anhychlorhydria in 6.

To be continued.

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

TWENTY-SECOND ANNUAL GENERAL MEETING

THE TWENTY-SECOND ANNUAL GENERAL MEETING was held at Liverpool on Friday and Saturday, May 25 and 26, 1928, in the Liverpool Medical Institution. The proceedings began at 10 a.m.

The President, Professor James Lindsay, was in the Chair.

The minutes of the last Annual Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

Election of Officers.

President. Professor J. Hill Abram was elected President for 1928–9. On his election he took the Chair and expressed the thanks of the Association to the retiring President for his services during the past year.

Honorary Member. Professor James Lindsay was elected an Honorary Member.

Election of Officers, members of the Executive Committee, and new members followed.

Treasurer. Dr. H. Morley Fletcher.

Secretary. Dr. H. Letheby Tidy.

Members for England:

Dr. Carey Coombs.
Dr. J. W. McNee.
Dr. J. C. Matthews.
Professor A. Ramsbottom.
Dr. J. A. Ryle.
Dr. R. A. Veale.

Members for Scotland:

Dr. L. Findlay.
Dr. R. A. Fleming.
Professor A. Patrick.

Members for Ireland:

Dr. S. B. Boyd Campbell.
Professor T. G. Moorhead.
Dr. W. A. Winter.

ASSOCIATION OF PHYSICIANS

New Members.

Leonard ABRAHAMSON, M.D., Physician, Mercer's Hospital, Dublin.

Walter Russell BRAIN, M.D., Assist. Phys., London Hospital.

Norman Brandon CAPON, M.D., Physician, Royal Southern Hospital, Liverpool.

Leybourne Stanley Patrick DAVIDSON, M.D., Assist. Phys., Leith Hospital.

Donald HUNTER, M.D., Assist. Phys., London Hospital.

Cyril Gray IMRIE, M.D., Assist. Phys., Sheffield Royal Hospital.

Douglas MCALPINE, M.D., Physician for Nervous Diseases, Middlesex Hospital.

Robert MARSHALL, M.D., Assist. Phys., Royal Victoria Hospital, Belfast.

Noah MORRIS, M.D., Assist. Phys., Royal Hospital for Sick Children, Glasgow.

Hugh Spear PEMBERTON, M.B., Physician, David Lewis Northern Hospital, Liverpool.

Samuel Ireland TURKINGTON, M.D., Assist. Phys., Royal Victoria Hospital, Belfast.

Herbert Lindesay Watson WEMYSS, M.D., Assist. Phys., Royal Infirmary, Edinburgh.

Presentation of Treasurer's Accounts. Dr. Morley Fletcher presented the Annual Accounts, which were adopted. They showed a balance of £152 4*s.* 10*d.*

Annual General Meeting in 1929. A letter was read from Sir Humphry Rolleston inviting the Association to meet in Cambridge in 1929. The invitation was cordially accepted.

Increase of Subscription. The Treasurer moved that the annual subscription be increased from 30*s.* to 40*s.* The contribution to the *Quarterly Journal of Medicine* had been increased last year by 10*s.* a member, and this necessitated an increase in the subscription. The motion was seconded by Dr. Tidy and passed unanimously.

Retirement of Sir Archibald Garrod as Editor of the Journal. On the motion of the President, a cordial vote of thanks was accorded to Sir Archibald Garrod for his long services.

Senior Members. The question of creating a special group of senior members was briefly discussed.

The Executive Committee had considered this with the object of providing for certain senior members, many of whom were original members who were anxious not to sever their connexion with the Association, but who now found difficulty in regular attendance. Members were asked to consider the matter.

SCIENTIFIC BUSINESS.

Friday Morning Session.

1. Dr. H. Wallace Jones on 'The Electrical Axis of the Heart as an Indicator of Changes in Ventricular Preponderance'. He used the graphic method for calculating the electrical axis, and showed the changes which took place with deep respiration in normal subjects, and the effect of adherent pericardium in limiting these changes. The changes in the axis in the early weeks of life, in complete transposition, in pneumothorax, and when there were changes in the cardiac rhythm, were also shown.

2. Dr. F. J. Poynton and W. P. Sheldon (introduced) on 'A Case of Coarctation of the Aorta with supervention of Malignant Aortitis in a Boy of 8 years'. The case was admitted with the diagnosis of typhoid. A large external mammary artery was

detected on the right side, but no other enlarged vessels. A haemolytic streptococcus was isolated from the blood. At autopsy, coarctation of the aorta was found, with an ulcer beyond the constriction. Section showed numerous streptococci on the surface of the ulcer. There were two aortic cusps but no endocarditis.

The case was discussed by Sir Thomas Lewis, Professor Murray, Drs. Parkes Weber, Wardrop Griffith, Starling, and W. Gordon.

3. Dr. M. A. Cassidy described 'A Case of Carotid Body Tumour associated with Syncopal Attacks'. There had been six syncopal attacks during four years, and the patient, a man aged 30, had noticed a small lump on the left side of the neck one year ago. Pressure on this lump slowed or stopped the heart and caused syncope. The tumour was excised with complete recovery and no further syncopal attacks. The tumour resembled adrenal cortex, and was considered to be malignant; no chromaffin tissue was demonstrated in it. Three similar cases had been discovered in the literature out of a total of some 100 recorded cases of carotid body tumour.

Sir Thomas Lewis inquired as to the blood-pressure. In the region of the carotid body there is a very sensitive control of the blood-pressure, which is supposed to control the blood-pressure to the brain.

Drs. Lakin, French, and Gaskell joined in the discussion.

4. Drs. C. E. Herapath and C. B. Perry (introduced) on 'A Case of Familial Sudden Death'. This family was described to the Association by Dr. Carey Coombs in 1924. The present case had had anginal attacks of increasing frequency for nine years. He died suddenly in a tramcar. He had been twice examined during life and no abnormal physical signs were found. At the post-mortem all the organs were healthy, with the exception of the heart and aorta. The aorta on section showed intimal thickening, with sub-intimal lipoid deposit. There was very little calcification. The heart, after coronary injection, showed an extreme degree of the age changes described by Gross.

5. Dr. John Cowan on 'Some of the Causes of Auricular Fibrillation'. Auricular fibrillation may persist until death after its first occurrence, or it may be paroxysmal. This variation in the clinical habits suggests a variation in the causation. He suggested that in man fibrillation might be produced by toxic causes which might, if sufficiently strong, produce the disturbance in a healthy heart.

Dr. John Hay believed that trauma and emotional shock were causes of auricular fibrillation.

Dr. F. J. Poynton described a case of congenital auricular fibrillation which was thought to be due to indigestion from milk.

Drs. Carey Coombs, Parkes Weber, Edgecombe, and Parkinson joined in the discussion.

6. Dr. J. A. Ryle, in discussing 'Angor Animi, or the Sense of Dying', laid particular stress on the organic nature of the symptom, insisting on its differentiation from morbid fear and anxiety. He described its occurrence in many conditions. The common factor in these was probably a powerful stimulus involving the medullary nuclei.

2–3 p.m.

Exhibition of clinical cases in the Medical Institution. Pathological and other demonstrations in the School of Hygiene.

Afternoon Session. 3 p.m.

1. Dr. H. Cohen (introduced) gave an account of 'Calcification of the Falx Cerebri'. It is easily demonstrable by radiography, and its presence may be suspected from a

fairly constant clinical syndrome. Whilst many cases are developmental in origin, the commonest associated pathological lesion is infection in the cranial air sinuses or the skull itself.

2. Sir James Purves-Stewart gave a lantern demonstration of 'Ventriculograms in Intracranial Tumours'. The technique of the introduction of air into the ventricles was described. The lumbar route, whereby the cerebro-spinal fluid is replaced by sterilized air, is preferable in most cases. In infra-tentorial and basal growths direct ventricular puncture is indicated. The technique of this was described, together with the special instrument for the purpose, whereby the procedure can be carried out under local anaesthesia. Illustrative ventriculograms were shown from cases.

3. Dr. F. Parkes Weber described 'A Case of Osteosclerotic Anaemia and Leukaemia'. The patient was aged 56 years, and showed extreme anaemia, the blood containing variable proportions of myelocytes and myeloblasts. Skiagrams showed a woolly appearance of some of the bones. Autopsy showed a condition of generalized osteosclerosis or endosclerosis of bone. The condition of the spleen, liver, and lymph-glands was not that of any kind of leukaemia. The diagnosis was discussed.

4. Lord Dawson of Penn contributed 'Some Further Observations on Acholuric Jaundice'. When the diagnosis has been made, splenectomy should be performed without delay, as the condition may become acute at any time. Of 11 cases operated upon, all were well, while of 11 cases without operation 4 had died, all with haemolytic anaemia. Some cases resembling, but not quite typical of, pernicious anaemia are probably later phases of acholuric jaundice. There is no clinical demarcation between 'congenital' and 'acquired' forms. The fragility, even after operation, never becomes normal.

Professor H. van den Bergh agreed with Lord Dawson's opinions.

Dr. Poynton mentioned a family in which one member showed no increased fragility.

Drs. Claude Wilson and Parkes Weber also spoke.

5. Dr. W. Howel Evans (introduced) on 'The Platelet Factor in Splenic Anaemia of the Banti type'. Prominent features in splenic anaemia are thrombosis in the splenic and related portal and mesenteric veins, and tendency to haemorrhages. He agreed with Rosenthal that the cases could be grouped according to the platelet count before splenectomy and the behaviour of the platelets afterwards. One group showed thrombopenia and a marked tendency to haemorrhage. After splenectomy the platelets rose for a short time and then fell to normal, the patients being restored to good health. The other group showed normal or rather high platelet counts before splenectomy, and following operation a massive rise of the platelets persists until fatal mesenteric thrombosis occurs.

6. Dr. S. W. Patterson reported 'A Case of Human Infestation with Liver Fluke and Observations on Eosinophilia' in a man of 43 years. There were mild rigors, with irregular fever and sweats, and at times colic. The blood showed a leucocytosis of 18,000 per c.mm. with 11,000 eosinophils (62 per cent.). X-ray examination of the chest and alimentary tract was negative. Numerous ova of *Fasciola hepatica* were found in the stools. Hexamine was given by the mouth, concentrated magnesium sulphate twice a week, and a course of injections of stibosan intravenously. The abdominal symptoms disappeared, but some eosinophilia persisted.

7. Dr. A. G. Yates on 'Cerebral Embolism due to an Ununited Fracture of the Clavicle and Subclavian Thrombosis'. A woman of 41 gave a history of pain and weakness in the right hand and forearm, aggravated by movement. The hand was blue and cold. No pulse could be felt in the limb. A radiogram showed an ununited fracture of the clavicle. Before treatment could be carried out, a cerebral embolus occurred and was fatal. At autopsy the fractured bone appeared to have compressed the subclavian, in which two firmly organized thrombi were found. The basilar

artery was completely blocked at its bifurcation. The thrombosis had extended backwards, and a detached portion had travelled as an embolus to the brain.

Dr. Symonds mentioned two cases of cervical ribs with similar effects.

Saturday Morning Session.

1. Dr. A. B. Soltau reported 'A Case of Pneumo-ventriculosis'. The patient, a lady aged 60, had a brief febrile illness, with running from the nose. Subsequently indefinite symptoms suggesting encephalitis developed. The right antrum was found to be infected and was punctured and washed out. As the patient improved, she complained of a clicking noise in the head which was brought out by nodding movements and was audible to observers. A radiograph showed that the right lateral ventricle was practically completely distended with air. There was no sign of air in the third or left lateral ventricles. The rhinorrhoea was found to be due to cerebrospinal fluid. Recovery has been complete. The cause remained obscure. No history of trauma was obtainable.

Sir James Purves-Stewart believed that the air was forced through the cribriform plate.

Dr. Gordon Holmes said that it was not uncommon after slight trauma.

2. Dr. A. R. Parsons described 'A Case of Myelopathic Albumosuria' in a man aged 47 years, who complained of pain in the upper part of his chest of eight weeks' duration, pain in the legs, loss of appetite, vomiting, and emaciation. On examination, two tumours as large as walnuts were palpable on the ribs. The urine presented the typical features of myelopathic albumosuria. The autopsy disclosed marked fragility of the ribs, with tumours on several of them and elsewhere. These tumours were plasmo-cytomata. The disease is very rare in Ireland.

Drs. Abrahams, Hurst, Parkes Weber, and Nattrass discussed this communication.

3. Professor Craven Moore and Dr. W. Morrell Roberts (introduced) on 'The Diagnostic Significance of HCl and of Lactic Acid in the Stomach-contents in Cancer of the Stomach'. Fractional gastric analysis in 22 cases of verified carcinoma of the stomach showed achlorhydria in 77 per cent., hyperchlorhydria in 9 per cent., lactic acid in 50 per cent. Lactic acid had never been found in the stomach-contents apart from carcinoma; its presence had no relation to gastric stasis. It was found earlier and more frequently in rapidly growing types of neoplasm, and no evidence of bacterial fermentative origin had been determined. The presence of lactic acid in the stomach-contents is pathognomonic of carcinoma of that organ, and it probably arises by the specific activity of the cancer cells on glucose in the tissue fluids.

Dr. Hurst stated that achlorhydria was present in only 60 per cent. of his cases.

Professor MacLean, Drs. Graham, Bennett, Tidy, and others joined in the discussion.

4. Professor Hugh MacLean on 'Some New Observations on Gastric Secretion'. It is generally held that regurgitation of alkaline intestinal contents into the stomach is the main factor in reducing the hydrochloric acid present during the later stages of digestion. Such regurgitation, if it took place, should be accompanied by (1) increase of CO_2 in the gastric contents, (2) presence of trypsin and bile in the gastric contents. Experiments show that no increase of CO_2 is found and no evidence of the presence of trypsin. Investigations show that the stomach itself secretes sodium chloride, and that the increase of sodium chloride found at the end of digestion is due not to neutralization of hydrochloric acid by regurgitated sodium bicarbonate, but to an increased secretion of salt in the stomach. The decrease of acid and increase of salt which characterizes the later phases of gastric digestion is seen in an isolated Pavlov pouch in a dog. Here there is no possibility of regurgitation. The acid secretion is regulated automatically and there is no evidence of any appreciable regurgitation of intestinal contents in ordinary digestion.

Dr. Bolton did not agree that the acidity of the gastric contents is lowered in the later stages of digestion by the gradual replacement of the HCl of the secreted gastric juice by neutral chloride. He agreed that in certain conditions, at present unknown, neutral chloride passes through the mucous membrane of the stomach, but there is no evidence to show that the acidity of the gastric contents is regulated by this means. MacLean's work with the Pavlov fistula contradicts his own hypothesis. According to his experiments, as the secretion of gastric juice falls off in amount the HCl contained in it is gradually replaced by neutral chloride, but after three hours, when the secretion is practically stopped, its acidity is still in the neighbourhood of 0·22 per cent. In other words, as the stomach is emptying the acidity of the gastric juice gradually falls from about 0·5 to 0·22 per cent., when the secretion stops. So long as an effective juice is secreted its acidity is above 0·22 per cent. When this juice acidity begins to fall there is in the stomach a variable amount of food of an acidity of, say, 0·15 to 0·2 per cent., which will have left the stomach by the time the juice acidity has dropped to 0·22. If duodenal regurgitation be excluded, the only fluid mixing with this food is the secreted gastric juice, the acidity of which is, during the whole time, higher than that of the food. How can this secretion of gastric juice into the food lower the acidity of the latter? The unaided gastric juice, however much neutral chloride it may contain, is unable to cause a fall in the acidity of the gastric contents. Some other factor is necessary, and that is regurgitation of duodenal contents.

Professor MacLean, in reply, upheld the correctness of his conclusions.

5. Dr. A. F. Hurst on 'Some Disorders of the Oesophagus'. As he had suggested in 1914, achalasia of the cardia has now been proved to be due to disease of Auerbach's plexus preventing the normal relaxation of the cardiac sphincter when each peristaltic wave reaches it during deglutition. Dr. Hurst then described a symptom-complex consisting of difficulty in the initiation of swallowing, associated with atrophic glossitis, severe secondary anaemia, and sometimes splenomegaly. A probable explanation is that the glossitis, which is associated with a similar condition at the pharyngo-oesophageal junction, is due to a streptococcal infection which leads to the anaemia and splenomegaly, and that the inflammation of the mucous membrane spreads to the local nerve tissue controlling the sphincter formed by the aryteno-pharyngeus muscles, so that it does not relax in the first stage of deglutition, a condition which would be exactly analogous with achalasia of the cardia.

Dr. Harry Campbell referred to oesophageal flatulence as a cause of cardiac disturbance.

Professor Douglas Stanley and Dr. Poulton also spoke.

Dr. Hurst, in reply, believed that oesophageal flatulence is caused by aerophagy.

6. Dr. A. G. Gullan described 'Two Cases of Adiposis Dolorosa'. Both were women, aged about 50, who developed masses of fat on the upper arms and thighs, and an apron of fat on the lower abdomen. They complained of asthenia and of various pains in the regions affected. The face, neck, hands, and feet were quite free from fat. The Wassermann test was negative, and the sella turcica was normal, by X-ray. One patient died, and at the autopsy the thyroid was fibrous and small; the pituitary gland was normal. Dr. Gullan's view is that thyroid deficiency is the main cause of this condition.

Several members discussed this communication.

7. Dr. Geoffrey Evans described 'The Clinical Picture of Spastic or Irritable Colon'. This is a chronic general spasm of the colon. Constipation and flatulence are the common features, the latter largely dependent on the use of laxatives. Abdominal discomfort is characteristically right-sided or may amount to actual pain localized to the colon. On examination the colon is easily palpable, and with a barium meal deep haustrations are seen in the transverse colon. The condition is a peripheral and not a central neurosis. Treatment is by rest, warmth, belladonna, and a low-residue diet.

2 p.m.–3 p.m.

Exhibition of clinical cases in the Medical Institution.

Pathological and other demonstrations in the School of Hygiene.

Afternoon Session. 3 p.m.

1. Dr. O. Leyton reported 'Two Cases of Pluriglandular Disease associated with Tumour in the Thymus Gland'. Both cases were males, aged 11 and 31. The younger was pigmented and grew hair upon his upper lip and chin. Both deposited fat around face and neck, and developed glycosuria and hyperglycaemia. The younger had epileptiform fits towards the end, the elder became mildly maniacal. At the autopsies, new growths were found in the thymus glands. The suprarenal glands were nearly twice the average weight for bodies of same age and weight. The cortices were hypertrophied, whilst the medullary areas were atrophied. The thyroid glands were hypertrophied.

Drs. Langdon Brown and Parkes Weber discussed this communication.

2. Dr. L. S. T. Burrell communicated his results with 'Sanocrysin in the Treatment of Pulmonary Tuberculosis'. He had treated sixty cases. Of twenty-eight cases in a group 'not getting on', nineteen improved and fifteen lost bacilli from the sputum. Improvements also occurred in cases relapsing after artificial pneumothorax and in other cases. Sanocrysin apparently precipitates a temporary healthy state but does not prevent recurrences. It is useful in acute cases not of great severity. He used an initial dose of 0·1 grm., increasing to 1 grm. Serious complications are avoided by regulating the dose. Serum produced no benefit.

Dr. Chandler stated that of twenty-five cases nine did well. He aimed at a total dosage of 5 grm.

3. Professor W. E. Dixon and Dr. S. E. Gooding (introduced) on 'Acute Pulmonary Oedema'. Referring to cardiac cases, in which the condition must be due to changes in the circulation, the initial cause is a rise in pulmonary pressure. There are two clinical groups: (1) following aspiration and probably due to stimulation of the vagus, (2) idiopathic with a sudden onset and no apparent cause. This second group can be imitated experimentally by a drug. This drug causes dilatation of the coronary vessels and produces oedema by a rise in pulmonary pressure.

Drs. Wall, Poynton, Nesbitt, and Parkes Weber discussed this communication, and Professor Dixon replied.

4. Professor J. Douglas Stanley described 'An Unusual Case of Typhoid Fever'. The onset was sudden and the right base became consolidated. There were no spots or enlargement of the spleen. The blood and fluid from the right pleural cavity gave a positive Widal reaction. At autopsy, *B. typhosus* was isolated from the lung.

5. Dr. C. G. Lambie on 'Pituitrin and Intermediary Carbohydrate Metabolism'. 50 grm. of glucose injected intravenously into the normal subject caused a rise in the oxygen consumption and in the respiratory quotient, the highest values being obtained at the end of half an hour. As the oxygen consumption rose, the inorganic blood phosphate fell, and the injected sugar disappeared from the blood. When a similar experiment was carried out in the diabetic, little, if any, rise in the respiratory quotient and oxygen consumption might be observed, and the fall in the blood phosphate was correspondingly less marked, while the injected sugar took longer to disappear from the blood. When pituitrin (0·75–1 c.c.) was injected immediately before the intravenous administration of glucose in the normal subject, the results resembled those in the diabetic subject. These observations supported the view that pituitrin exerted an action antagonistic to that of insulin.